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INTERNATIONAL RECORD OF MEDICINE

THE MEANING OF GREATNESS:
SIR ALEXANDER FLEMING—IN MEMORIAM

EDITORIAL SURVEY

CHEMOTHERAPY OF CANCER

SYMPOSIA ON NEW FACTS AND PERSPECTIVES OF BROAD-SPECTRUM ANTIBIOTIC THERAPY

I—OXYTETRACYCLINE

Guest Editor—MERLE M. MUSSELMAN, M.D.

PART 2

OXYTETRACYCLINE IN DERMATOLOGY AND SYPHILOLOGY — *Harry M. Robinson*

THE USE OF OXYTETRACYCLINE IN INFECTIONS OF BONES AND JOINTS AND THEIR SOFT-TISSUE COVERINGS — *J. Buchman*

OXYTETRACYCLINE AS AN ADJUNCT TO SURGICAL THERAPY IN ESTABLISHED PERITONITIS AND PERITONEAL CONTAMINATION — *Prigot and Maynard*

OXYTETRACYCLINE IN OBSTETRIC INFECTIONS — *H. Close Hesseltine*

OXYTETRACYCLINE IN THE TREATMENT OF PELVIC INFECTIONS — *George Blinick and Samuel Soichet*

OXYTETRACYCLINE IN THE TREATMENT OF INFECTIONS OF THE GENITOURINARY TRACT — *William C. Baum*

INTRAMUSCULAR OXYTETRACYCLINE IN THE TREATMENT OF ACUTE GONORRHEAL URETHRITIS IN THE MALE — *Milton Marmell and Aaron Prigot*

OXYTETRACYCLINE IN OPHTHALMOLOGY — *Joseph W. Hallett and Irving H. Leopold*

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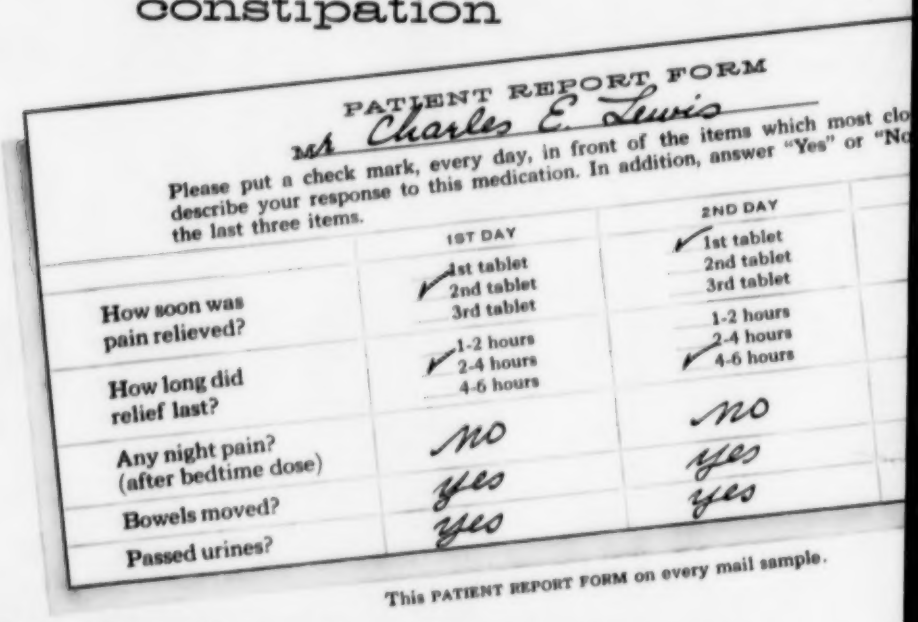

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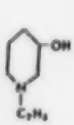

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VOL. 168 NO. 4 • WHOLE NUMBER 2866 • APRIL 1955

The Meaning of Greatness: Sir Alexander Fleming—In Memoriam 199
Félix Martí-Ibáñez

The Life of Sir Alexander Fleming 202

EDITORIAL SURVEY

Chemotherapy of Tuberculosis 204

Symposia on New Facts and Perspectives of Broad-Spectrum Antibiotic Therapy

I—Oxytetracycline

Guest Editor—MERLE M. MUSSELMAN, M.D.

PART 2

Oxytetracycline in Dermatology and Syphilology 207
Harry M. Robinson, Jr.

The Use of Oxytetracycline in Infections of Bones and Joints and Their Soft-Tissue Coverings 213
J. Buchman

Oxytetracycline as an Adjunct to Surgical Therapy in Established Peritonitis and Peritoneal Contamination 220
Aaron Prigot and Aubre de L. Maynard

Oxytetracycline in Obstetric Infections 229
H. Close Hesseltine

Oxytetracycline in the Treatment of Pelvic Infections 238
George Blinick and Samuel Soichet

Oxytetracycline in the Treatment of Infections of the Genitourinary Tract 248
William C. Baum

Intramuscular Oxytetracycline in the Treatment of Acute Gonorrheal Urethritis in the Male. 254
Milton Marmell and Aaron Prigot

Oxytetracycline in Ophthalmology: A Review of the Literature 257
Joseph W. Hallett and Irving H. Leopold

GENERAL PRACTICE CLINICS

Nasal Hydrocortisone in Allergic Rhinitis: A Controlled Study 271
Henry D. Ogden, Huldah Bancroft, Jack Ruli, Cecil Branzon, and C. A. Bodet

Cortisone or Hydrocortisone in the Treatment of Severe Intractable Bronchial Asthma 272
Walter S. Burrage, David M. D. Wang, John W. Irwin, and Saul Aronow

Gonorrhea in the Female 272
George W. Mitchell

Current Status of Rauwolfia Preparations 273
George A. Hellmuth

The Enlarged Spleen 275
Milnes Walker

Gonorrhea in the Male 275
B. G. Clark

The Tongue in Health and Disease 276
Leo Stern

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RECORD OF MEDICINE

VOL. 168 NO. 4 • WHOLE NUMBER 2866 • APRIL 1955

The Meaning of Greatness

SIR ALEXANDER FLEMING—IN MEMORIAM

Félix Martí-Ibáñez, M.D.
NEW YORK, N. Y.

Greatness is simplicity. "To be great," said Nietzsche, "is to point out new directions . . ."—we might add, to point them out with elegant simplicity. The death of Sir Alexander Fleming, a great man of great simplicity, invites us to meditate once again—while his remains are barely cold and the tears shed in his memory still fresh—on the meaning of greatness.

It is a sad if glorious privilege of the great scientific conceptions of the human mind that no sooner are they incorporated into man's treasure store of wisdom than they eclipse their creators. Artistic creation, on the other hand, is linked inextricably with the personality of the creator. It is impossible to hear the chords of the *Eroica* without evoking the pensive, leonine head of Beethoven; one cannot read a page of *Don Quixote* without recalling the undaunted hero of Lepanto who penned it; one cannot gaze upon the polychrome flashes of the *Night Watch* without seeing the melancholy figure of Rembrandt.

But this is not true of scientific creation. As it grows it becomes more and more impersonal, until finally it detaches itself completely from the person of its creator. How many people inoculated with smallpox vaccine know the name of Jenner; how many tubercular patients could identify Koch; how many luetics have given a thought to Ehrlich? Scientific achievements, unlike artistic achievements, do not endure in terms of their authors; the scientist himself feels subconsciously that his glory is transitory, that his name will vanish as soon as the formula, the medicine, or the heavenly body he discovered passes into common domain. The more concrete are the outlines of his work, the more indistinct does his personality, and even his name, become in the mists of time.

But in the history of modern medicine, Fleming is the one scientist whose name and personality are most often recognized in connection with his scientific accom-

plishments. Not long ago I was having luncheon with Sir Alexander and Lady Fleming in Rome. On the table, fragrant fruits were piled high in golden wicker baskets garnished with fresh greens. Sir Alexander had just returned from my native Spain and his eyes were still aglow with the heavenly lights of Andalusia. Everywhere in the dusty villages people had kissed his hand as they would that of a saint; even the gypsies milled around his car on the dusty roads to Granada to catch a glimpse of him. In Athens he attended a performance of *Medea*. When he went backstage to compliment the star, she fell to her knees and, with tears misting her eyes, she said: "If it had not been for *your* penicillin, I would not be alive to perform in this theatre today."

Fleming became in his lifetime what few scientists ever become: a universal symbol of wisdom and goodness, a symbol of that "science which, had it no conscience, would be nothing but baseness of soul," as Montaigne, that jeweller of philosophic verities, once said. People perhaps sensed in this frail man, with limpid blue eyes, silvery white hair, and cheeks as rosy as dawn over the Scottish moors, the mystic presence of an apostle of science.

Perhaps the reason why Fleming's popularity transcended the limits of his achievements is that from the very beginning he was concerned with the *practical* application of penicillin. In 1928 a "fortunate accident" befell Fleming, as it has many other scientists not nearly so well prepared to convert the firefly of a chance discovery into a new star. Fleming once said: "Don't wait for Fortune to smile on you. Prepare yourself with knowledge. Then, if Fortune presents an opportunity, you will be able to take advantage of it." Yet ten years were to elapse before another scientist, Raistrick, reinvestigated penicillin, and two more years passed before other scientists, Florey and Chain, made practical clinical testing possible. The world rang with hope as it learned of the discovery that promised to liberate man from the cruelest scourge in history: infection. The scientist, who thus ushered in a new era in medicine, had wedded scientific observation to genius when he translated the vision of a laboratory investigator into a clinical reality.

Fleming's greatness was apparent from the very beginning in the simplicity of his person and of his conduct which accentuated all the more the magnitude of his discovery. Our times are bountiful in *big* men—in industry, in finance, in politics—but they can boast of few *great* men. Fleming revealed himself to be a *great* man in whom the very frailty of his small frame and the softness of his voice contrasted with the simple but gigantic ideologic framework which supported the inner structure of his personality.

What manner of research scientist was Fleming? I would say he was a naturalist —an investigator of the Hippocratic school, enamored of the ancient aphorism *Medicina tota in observationibus*, capable of doing what Darwin advised: to contribute to man's knowledge of Nature, not so much by an ability to deliver theoretical disquisitions, as by knowing how to count dexterously and correctly the tiny leaves of a plant.

A truly good investigator is more of a naturalist than an experimenter. This can be said of Fleming. Medicine has always been and should always be, above all, a science based on empirical observation. The physician should learn not only to see,

but to *look*, and he should then interpret correctly what he sees. Fleming discovered penicillin thanks to his training as a naturalist devoted to simple but consequential observation, the same training shared with Pasteur, Lister, Hunter, and Claude Bernard, not to forget Cajal and Pavlov and other great naturalists in medicine.

The famous "accident" that befell Fleming, when some humble spores carried by smoky winds through the grey skies of London fell on his culture plate, had certainly occurred before in other laboratories. But it required a mind endowed with unique vision to perceive that such an accident was the gold illuminated initial letter introducing a new and glorious chapter in the history of medicine. Fleming was guided by that "marvelous power of prolonged attention" recommended by Cajal.

Simplicity of thought, simplicity of feeling, simplicity in speech—all these gave meaning to Fleming's greatness. The form adopted by a scientific truth often becomes an integral part of the truth itself. Truth is, by definition, clear, and the art of expressing things clearly is of supreme importance in science. Scientific truth demands transparency, order simplicity, precision, and harmony. Hippocrates and Pasteur, Osler and Freud fulfilled this demand. So did Alexander Fleming.

The clarity of form which contrasts with the rich significance of his prose—a limpid lake of calm but deep waters—is another of his claims to fame. Fleming's work is written in a plain unadorned prose, comparable to that of Virgil's description of the swine plague in the *Georgics*. In Fleming's speeches and lectures, scientific thought was clad in a tunic of austere simplicity.

When a great man dies, the historical symbol is born. Antibiotics were introduced into modern medicine by Fleming's hand and were then transferred to the combined efforts of men and industry. As Fleming himself once said: "Who would have thought that a mold spore half the size of our blood corpuscles falling on one of my culture plates would eventually result in a large industry with factories employing thousands of people . . ."

As time goes on, scientific work becomes more depersonalized and it is finally remembered for its intrinsic value, not for the quality of the men who created it. But History bestowed upon Fleming the singular privilege of linking his name with his work as inextricably as Hamlet's profound words are associated with the genius of Shakespeare.

The Era of Antibiotics marches on with gigantic strides. Its progress is assured by complete depersonalization: the triumph of team work, complex instruments, well-appointed laboratories, and large-scale industries. But many years must pass before a patient treated with penicillin or the physician who administers it will forget the name of Fleming. This is the tribute to greatness, infinitely more solemn than any wreath, that History has laid upon his tomb.

THE LIFE OF SIR ALEXANDER FLEMING

1881 Born in a grey stone farmhouse at Lochfield, a small Ayrshire village about 16 miles south of Glasgow. His father farmed and also raised dairy cattle. Early schooling was in a moorland schoolhouse.

1894 Went to London to join his brother who was studying medicine. Continued schooling at the Regent Street Polytechnic but showed no particular interest in medicine. On leaving school, supported himself by working as a clerk. At this time he joined a swimming club run by the medical students at St. Mary's Hospital. Here he met Sir Almroth Wright, then head of the Inoculation Department at St. Mary's, who fired his interest in bacteriology. (Many years later, Sir Alexander said: "But for that encounter, I might never have become a bacteriologist.")

1902 Began studying at St. Mary's, winning the senior entrance scholarship in natural science. During his student years, he won nearly every class prize and scholarship offered.

1906 Worked as assistant to Sir Almroth in the Inoculation Department, acquiring great skill in bacteriologic technique and pathology.

1908 Qualified in medicine, obtaining honors and a gold medal in the M.B., M.S. examination.

1909 Became a Fellow of the Royal College of Surgeons.

1914 At the outbreak of war, was commissioned captain in the Royal Army Medical Corps and served four years in Wright's laboratory at Boulogne.

1915 Married Sarah McElroy with whom he had one son. Published his paper on "The Bacteriology of War Wounds," a standard work that was used again in World War II.

1919 Returned to St. Mary's Hospital in the post of lecturer in bacteriology and assistant to Sir Almroth.

1922 Attracted world-wide attention in medical circles for his identification of lysozyme which he cultured from the nasal secretion of a patient with acute rhinitis.

1928 Discovery and identification of *Penicillium notatum*. Lack of funds and facilities prevented further development.

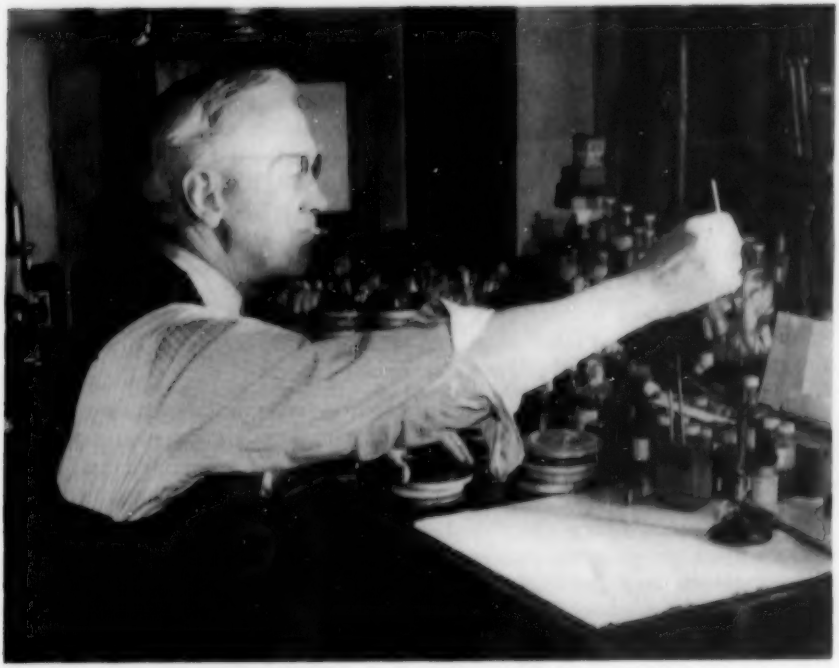
1932 Became president of the pathology section of the Royal School of Medicine. Continued to teach bacteriology at St. Mary's and at London University.

1943 After the work of Florey and Chain had launched penicillin on its fabulous career in clinical medicine, Dr. Fleming received countless honors.

1944 Made a Knight of the British Empire by the late King George VI.

1946 Shared the Nobel prize for medicine with Sir Howard Florey and Dr. Ernest B. Chain.

1947 On the death of Sir Almroth Wright, Sir Alexander succeeded him as head of the Inoculation Department at St. Mary's, now called the Wright-Fleming Institute of Microbiology.



Sir Alexander Fleming at work in his laboratory in a London hospital.

1949 Death of Lady Fleming, after 34 years of marriage.

1951 Elected rector of Edinburgh University.

1953 Married Dr. Amalia Coutsouris, a distinguished Greek research worker at the Wright-Fleming Institute.

1954 On the 25th anniversary of the discovery of penicillin, was presented with a pair of silver George III tureens by the Duke of Edinburgh on behalf of St. Mary's Hospital Medical School.

1955

January Retired from the post of principal of the Wright-Fleming Institute.
March 10 Attended at the Institute and discussed plans for an extensive lecture tour of the Middle East on behalf of the British Council.

March 11 The maid brought Sir Alexander his breakfast in bed. She last saw him reading his morning papers, as was his custom. He must have felt some uneasiness, for he telephoned his physician to come over. A few minutes later, the heart of a great yet unassuming researcher, a kindly teacher to whom so many scientists and physicians owe their training, had failed.

Editorial Survey

Chemotherapy of Cancer

The chemotherapy of neoplastic diseases is making relatively slow but steady progress and the days of random chemotherapeutic experiments appear to be over. The present approach is based on a better understanding of the mechanisms controlling cell growth and metabolism, and on a clearer conception of the metabolic differences between a normal cell and a malignant one.

The essential problem in biochemical research today is to discover some means, physical or chemical, of killing cancerous cells without injuring the healthy tissue of the host. The three main avenues now being explored are: starvation of the malignant cell, poisoning of this type of cell, and inhibition of its growth and motility.

In the first approach to the problem, the greatest interest appears to be in the folic acid antagonists developed by the late Dr. Y. Subbarow and his co-workers in 1947. These substances are basically composed of a pteridine nucleus linked to a para-aminobenzoic acid structure. Folic acid and its biologically active form, the citrovorum factor, are needed in the nutrition of all tissues, but are required in higher concentrations in tissues which are rapidly growing. Since it is now known that malignant cells multiply faster than normal ones, the possible "starvation" mechanism of such folic acid antagonists as aminopterin, A-methopterin, and adenopterin can be partially understood.

The most encouraging results obtained with these antagonists have been in the treatment of acute leukemia in children. Farber's[1] compilation of data on seven studies showed a 68.5 per cent improvement among 425 children treated for acute leukemia with these compounds. In the treatment of solid tumors, sarcomas, and carcinomas, some improvement has been obtained, particularly in patients with carcinoma of the breast or bladder. The toxicity which may attend antifolic therapy includes mucous membrane ulcerations, gastrointestinal disturbances, leukopenia, bleeding from the intestinal tract, and alopecia. Some adult patients have, however, been treated for two or three years with no apparent harmful effect.

Another antimetabolic agent which has shown encouraging results in the therapy of leukemia is 6-mercaptopurine, a purine antagonist. Burchenal[2] reported that the use of this compound in 68 children with acute leukemia had produced remissions in 29, partial remissions in 14, and failures in 25. In a series of 44 adults with the same disease, five showed clinical and hematologic remissions. The most frequent side effect from this purine analogue is leukopenia.

In the group of "poisoning" agents, the main interest centers around the nitrogen

mustards, one of which was the notorious mustard gas of World War I. As early as 1946, one of these compounds showed some beneficial effect on human lymphosarcoma. The outstanding feature of this group of cytotoxic agents is the ability to function as alkylating agents in mild conditions of living tissues. In the forefront of clinical research at present is methylbis (beta-chloroethyl) amine, called HN_2, which has provided temporary relief in Hodgkin's diseases, lymphosarcoma, the chronic leukemias, polycythemia rubra vera, and bronchogenic carcinoma. The general result was a reduction of tumor size and an improvement of symptoms produced by neoplastic infiltrations. However, the use of these mustards is restricted by their clinical toxicity, both local and systemic. Local effects at the site of injection include inflammation, thrombophlebitis, and tissue necrosis. The immediate systemic effects are largely gastrointestinal, while the delayed effects of HN_2 include damage to elements of the hemopoietic system.

Among the ethylene-imines which have shown interesting clinical results are triethylene melamine, triethylene phosphoramide, and triethylene thiophosphoramide. It is interesting to note that triethylene melamine was first produced in Germany during the last war to improve the finish of rayon fabrics. Subsequently, Rose[3] and co-workers discovered that this substance inhibited the growth of a Walker rat carcinoma. In a controlled study of 71 cases with incurable neoplastic diseases treated at Harlem Hospital,[4] total remission was obtained in 8 cases and improvement in 33 cases; the complete remissions lasted from 56 days to three years.

Other chemotherapeutic agents of value in some neoplastic diseases include myleran, which has improved patients with chronic granulocytic leukemia, and urethane, which has some effect in leukemia. Potassium arsenite (Fowler's solution) also continues to demonstrate fairly good results, especially in chronic myelogenous leukemia.

The chemotherapy of cancer now includes the hormones: ACTH, cortisone and its analogues, testosterone, and the estrogens. Since 1949 it has been known that ACTH could produce complete remissions in the acute leukemias of children. Both ACTH and cortisone are of value in the leukemias, the treatment of lymphosarcoma, and Hodgkin's disease, but these remissions are generally shorter than those obtained with the folic acid antagonists. For this reason they are customarily reserved for the extremely ill patients.

In the control of inoperable cancers of the female breast, some androgens and estrogens have produced encouraging results, although primarily palliative ones. In its 1951 report on 886 cases of advanced mammary cancer,[5] the American Medical Association's subcommittee on steroids found that both testosterone and estrogen produced improvement lasting from 10 to 12 months in soft tissue lesions, and from 11 to 18 months in bony lesions.

The most recent entry into the field of cancer chemotherapy is the antibiotic puromycin, isolated from a strain of Streptomyces, which has produced some objective evidence of improvement in patients with disseminated or advanced neoplastic diseases. Work is also in progress in several laboratories on the possible tumor-inhibiting activity of other antibiotics.

It would be a marvel indeed if the already astonishing "antibiotic age" were to be crowned with the final conquest of cancer. The last decade has certainly shown that the potentialities of chemotherapy are far from being exhausted.

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Symposia on New Facts and Perspectives of Broad-Spectrum Antibiotic Therapy

I. OXYTETRACYCLINE

Guest Editor—Merle M. Musselman, M.D.

Part 2*

Oxytetracycline in Dermatology and Syphilology

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Oxytetracycline (Terramycin†) has proved to be a potent weapon with which the physician may successfully combat some diseases, for which no satisfactory means of therapy previously existed. This agent is of value in the treatment of many cutaneous diseases both by oral administration and by local application. The dermatologist must have a thorough knowledge of the indications, contraindications, and limitations of this broad-spectrum antibiotic. Answers to these problems may be determined only by careful statistical studies by trained investigators. During the past five years, a team of trained, certified dermatologists working in our department at the University of Maryland has been compiling statistics in an attempt adequately to evaluate antibiotics in the treatment of dermatoses. Studies on oxytetracycline have been conducted on 1,706 patients, and this present report represents an interpretation of our statistical survey.

TOPICAL USE OF OXYTETRACYCLINE

Oxytetracycline ointment proved to be of definite value in the treatment of the pyodermas. The results of topical treatment may be divided into three categories: those conditions definitely benefited (table I); conditions occasionally, partially, or temporarily improved (table II); and conditions not improved (table III). Thus, among the dermatologic conditions in which topical oxytetracycline therapy as a rule produced good results were ecthyma (131 of 146 cases), impetigo contagiosa (165 of 191), pyoderma (61 of 70), dermatitis repens (35 of 39), and sycosis vulgaris (21 of 29). In many conditions complicated by secondary pyogenic infection, the preparation caused rapid eradication of the pyoderma but had no effect on the primary condition. Fungus infections did not respond to this medication. For topical application, the ointment was dispensed in a base consisting of liquid petroleum

* Part 1 appeared in the March, 1955, issue of International Record of Medicine and General Practice Clinics.

† The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

TABLE I

Conditions Definitely Benefited by Topical Application of Oxytetracycline

Disease	Total Cases	Good Results	Poor Results	Improved, No Follow-up	No Follow-up	Shortest Time for Good Results	Longest Time for Good Results	Adverse Reactions
Abscess, draining	11	11				7 days	14 days	
Acne varioliformis	1	1				7 days		
Dermatitis repens	39	35	1	1	2	9 days	24 days	1
Ecthyma	146	131	1	1	13	6 days	14 days	
Impetigo contagiosa	191	165		5	21	3 days	12 days	1
Paronychia, purulent	19	12	4	1	2	6 days	14 days	
Pyoderma	70	61	2	3	4	5 days	21 days	
Otitis externa	11	6	2	3		6 days	12 days	
Sycosis vulgaris	29	21	2	3	3	7 days	14 days	

in a concentration of 30 mg. to each gram of ointment base. Of the 1,016 patients, 11 developed local irritative reactions following the use of oxytetracycline ointment. Patch tests were positive in only 4 of these cases.

Use in Treatment of Dermatoses. In the treatment of pyodermas or conditions complicated by secondary pyogenic infection, patients were instructed to remove the crusts or surface exudate with warm water compresses twice daily prior to the application of the ointment. In all other entities, they were instructed simply to apply the ointment twice daily. The 3 per cent ointment was used in the treatment of 1,016 patients.

TABLE II

Conditions Occasionally, Temporarily, or Partially Improved by Topical Application of Oxytetracycline

Disease	Total Cases	Good Result	Partial Improvement	Temporary Improvement	No Improvement	Improved, No Follow-up	No Follow-up
Acne vulgaris	15		4		8		3
Atopic dermatitis, infected	45		13	24	1	6	1
Contact dermatitis, infected	112	11	90	4	3	2	2
Eczema, stasis, infected	5		2	1	2		
Epidermophytosis, infected	27	4	19	2			2
Folliculitis	14	3	2	2	2	2	3
Hydradenitis, infected	4		2	1	1		
Infant eczema, infected	29		16	7		3	3
Infected wounds and desiccation	9	2	7				
Infectious eczematoid dermatitis	61	17	3	18	4	9	10
Insect bites, infected	5			4			1
Perleche	4		2	2			
Seborrheic dermatitis, infected	37	4	21	6	3	1	2
Stasis ulcer, infected	6		3	1	2		
Sunburn, infected	3	3					
Tinea kerion	13	2	7			2	2

Topical Use of Oxytetracycline and Steroids. Recently a combination of oxytetracycline and hydrocortisone acetate in an ointment base has proved to be of definite value in the treatment of infected allergic dermatoses. The preparation used contained 0.5 per cent hydrocortisone acetate and 3 per cent oxytetracycline in an ointment base consisting of mineral oil and petrolatum. The value of hydrocortisone acetate in the local treatment of selected dermatoses has been demonstrated. The addition of oxytetracycline to the preparation has the additional advantage of treating any secondary pyogenic infection that may be present. The antibiotic does not alter the effect of the hydrocortisone, and the hydrocortisone does not impair the activity of oxytetracycline.

TABLE III

Conditions Not Benefited by Topical Application of Oxytetracycline

Disease	Total Cases	Disease	Total Cases
Atopic dermatitis	25	Molluscum contagiosum	3
Alopecia areata	3	Papular urticaria	7
Dermatitis venenata	9	Pityriasis rosea	5
Eczema chronic lichenoid (neurodermatitis)	9	Psoriasis	5
Eczema nummular	6	Rosacea	5
Eczema perianal	3	Scabies	4
Epidermophytosis	13	Seborrheic dermatitis	23
Epithelioma, basal cell	3	Seborrheic keratoses	2
Folliculitis decalvans	2	Tinea capitis	13
Fox-Fordyce disease	1	Tinea corporis	5
Granuloma annulare	2	Tinea cruris	2
Herpes simplex	4	Tinea versicolor	3
Herpes zoster	3	Verruca accuminata	3
Krauosis vulva	1	Verruca plana juvenilis	2
Lupus erythematosus, chronic discoid	2	Verruca plantaris	2
		Verruca vulgaris	5

TREATMENT OF DERMATOSES BY ORAL ADMINISTRATION OF OXYTETRACYCLINE

Orally administered oxytetracycline has proved to be of value in erythema multiforme, in granuloma inguinale, and in the treatment of all conditions that involved pyogenic organisms (table IV). It may be considered as an adjunct in the therapy of acne vulgaris and acne conglobata. It is not a definite curative measure because, in the large majority of cases treated, there was a recurrence of the eruption after the drug was discontinued. Four of the 9 patients with herpes zoster appeared to be benefited, but 2 of the remaining 5 developed severe postherpetic pain despite therapy. Many dermatoses complicated by secondary pyogenic infection, such as eczema, seborrheic dermatitis, epidermophytosis, and stasis ulcers, were improved by the medication in that the secondary infection was cleared. The primary condition, however, was not benefited (table V). A large number of dermatoses treated with oxytetracycline did not respond to oral administration of the drug (table VI).

TABLE IV

Conditions Definitely Benefited by Oral Administration of Oxytetracycline

Disease	Total Cases	Good Results	Poor Results	Improved, Incomplete Follow-up	No Follow-up	Smallest Dose, Gm.	Largest Dose, Gm.
Abscess	12	12				7	14
Carbuncle	4	3		1		14	16
Cellulitis	53	50		1	2	14	88
Erysipelas	4	4				14	26
Erythema multiforme	33	24	3	3	3	14	42
Erythema multiforme bullosum	14	12	1	1		14	50
Furunculosis	29	27	1	1		9	42
Granuloma inguinale	14	13			1	16	44
Hydradenitis suppurativa	24	18	1	2	3	15	58
Lymphangitis	31	27		3	1	16	30
Pyoderma	15	14		1		4	14
Paronychia	17	12		2	3	6	14

In this large series of patients no blood dyscrasias were noted. Nine individuals suffered nausea, 11 had nausea and vomiting, 5 had diarrhea, 2 had pruritus ani, and 1 had vague abdominal pain.

Dosage Schedules. All adults of average size were given an initial dose of 2 Gm.

TABLE V

Conditions Occasionally, Temporarily, or Partially Improved by Oral Administration of Oxytetracycline

Disease	Total Cases	Good Result	Partial Improvement	Temporary Improvement	No Improvement	No Follow-up	Smallest Dose, Gm.	Largest Dose, Gm.
Acne vulgaris	45	6	8	26	4	1	68	112
Acne rosacea	9			6	2	1	14	60
Acne conglobata	39	5	2	28	3	1	68	140
Aphthous stomatitis	4	1		2	1		5	43
Dermatitis herpetiformis	4	1		3			28	60
Eczema, infected	39		30	3	2	4	14	28
Epidermophytosis, infected	22		20	1		1	14	40
Erythema nodosum	4	1		3			7	14
Folliculitis	26	8	3	13	1	1	10	52
Folliculitis decalvans	3		2	1			12	28
Granuloma annulare	4		2	1		1	14	30
Herpes zoster	12	5			6	1	28	28
Infectious eczematoid dermatitis	31	8		11	7	5	85	48
Seborrheic dermatitis, infected	9		4	2		3	14	28
Stasis ulcers, infected	2		2				14	28
Sycosis vulgaris	16	5	4	6		1	14	40
Tinea capitis, infected	13	6	6			1	6	18

followed by 0.5 Gm. four times daily. If there was no improvement after two or three weeks of this therapy, the administration of the drug was discontinued. In some dermatoses that were definitely benefited by the use of oxytetracycline, it was possible to reduce the maintenance dose of the drug to 250 mg. four times daily and still retain a satisfactory result. This was particularly true in some cases of cystic acne vulgaris. Children less than 10 years of age were given an average dose of 50 mg./Kg. of body weight divided into four doses in a 24 hour period.

TREATMENT OF SYPHILIS BY THE ORAL ADMINISTRATION OF OXYTETRACYCLINE

Oxytetracycline given orally will cause the *Spirochaeta pallida* to disappear from the moist lesions of early syphilis in 24 hours. A series of patients with a positive

TABLE VI

Conditions Not Benefited by Oral Administration of Oxytetracycline

Disease	Total Cases	Disease	Total Cases
Acne keloid	1	Miliaria rubra	3
Alopecia areata	2	Molluscum contagiosum	4
Atopic dermatitis (eczema)	15	Otitis externa	4
Condylomata accuminata	4	Pityriasis rosea	10
Dermatitis venenata	6	Psoriasis	6
Eczema, lichenoid (neurodermatitis)	6	Rosacea	4
Eczema, nummular type	6	Sarcoid	2
Epidermophytosis	12	Scleroderma	2
Epithelioma	1	Seborrheic dermatitis	8
Herpes simplex	9	Tinea capitis	5
Keratosis follicularis	2	Tinea versicolor	3
Lichen planus	4	Trichophytosis corporis	3
Lichen sclerosis and atrophicus	1	Verruca plana juvenilis	4
Lupus erythematosus, chronic discoid	4	Verruca plantaris	3
		Verruca vulgaris	6

dark field and early syphilis were treated with oxytetracycline and given a total of 48 Gm. in divided doses over a 15 day period. All of these individuals were hospitalized to insure their receiving the medication as prescribed. At the end of one year, the follow-up survey indicated that 75 per cent of these patients had complete involution of lesions and negative serologic tests for syphilis. Twenty-five per cent had either mucocutaneous or serologic relapse. These results indicate that oxytetracycline is of definite value as an antisyphilitic agent. Any system of oral medication in syphilis is potentially dangerous because of the inconstancy of the patients in carrying out the advice of the physician. If oxytetracycline is used in the treatment of syphilis, the patient must be under constant supervision.

It is difficult to evaluate any drug in the treatment of latent syphilis unless the investigator has accumulated a large series of patients and has had them on constant follow-up observation for a minimum period of 10 to 15 years. The drug has not

been available for use for that period of time. The major indication for the use of oxytetracycline in the treatment of latent syphilis would be intolerance to penicillin or a history of sensitivity to that drug. In such an instance, oxytetracycline would be the drug of choice and the dose would be the same as that used in the treatment of early syphilis.

In benign late syphilis, oxytetracycline causes involution of gummas regardless of the location of the lesion. The recommended treatment period is 30 days with a total dose of 90 Gm. divided over that period.

In the treatment of cardiovascular syphilis and central nervous system syphilis the same treatment schedule should be observed as that used in the treatment of late benign syphilis.

CONCLUSIONS

1. Oxytetracycline ointment caused rapid healing of pyogenic infections, such as impetigo contagiosa and ecthyma. It was also of value in the treatment of many skin eruptions complicated by secondary pyogenic invasion, although it has no effect on the basic dermatosis.

2. The oral administration of oxytetracycline proved to be of value in the treatment of secondary pyogenic invasion of dermatoses, such as eczema, epidermophytosis, stasis ulcers, and seborrheic dermatitis, although it had no beneficial effect in the primary disease.

3. The oral administration of oxytetracycline proved to be of definite benefit in all conditions in which pyogenic organisms were the primary cause of the disease.

4. The lesions of granuloma inguinale healed rapidly following the institution of treatment with oxytetracycline orally, and no relapses have been noted.

5. The lesions of erythema multiforme responded to treatment with oxytetracycline orally in 17 of 24 cases.

6. Oxytetracycline is a valuable adjunct to syphilotherapy and should be used in those individuals who are sensitive to penicillin.

7. No blood dyscrasias were encountered in this series of cases treated with oxytetracycline orally.

8. This drug is a valuable addition to those already in use in the treatment of skin diseases. As with all antibiotics, this medication should be used only where there is a specific indication.

The Use of Oxytetracycline in Infections of Bones and Joints and Their Soft-Tissue Coverings

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INTRODUCTION

Oxytetracycline (Terramycin*) has attained a role of great importance in the prevention of infections and more significantly in the eradication of established infections of bones and joints despite its relatively recent introduction into the family of broad-spectrum antibiotics. Oxytetracycline is not a panacea nor a cure-all. Its use must be discriminate and rational if it is to be effective. Indiscriminate and irrational use of any drug, no matter how good, may result not only in failure but in actual damage and discredit.

The results of treatment of infections of bones and joints with oxytetracycline are superior to those obtainable in the days prior to the introduction of the broad-spectrum antibiotics. The complications incidental to its use are less than those incident to the use of other antibiotics. The failures that are still encountered notwithstanding the seemingly proper use of the antibiotic are attributable to one or more of four factors and their ramifications. These in the order of their importance and frequency are the following: (1) the nature and characteristics of the lesion encountered, (2) the nature of the offending microorganism, (3) the nature of the patient's response both to the bacterial invader and to the therapeutic agent, and (4) the method and intensity of administration of the antibiotic.

THE NATURE OF THE LESION

The nature of the lesion encountered in infections of bones and joints (osteomyelitis and pyogenic arthritis) and their covering structures can best be appreciated by visualizing the differences that exist between these surgical infections and the so-called medical infections. The medical infection is usually an inflammatory process with little or no necrosis or enclosed suppuration. Such a lesion by virtue of its increased blood supply remains in close contact with the blood stream. As a consequence of this any effective therapeutic agent may be introduced into the focus by way of the blood stream to exert its influence on the lesion. In surgical infections, such as those of the bones and joints, there is an inflammatory process upon which at an early stage are superimposed additional crucial phenomena. Among these are thromboses at the periphery of the lesion, which result in a walling-off process, and necrosis and suppuration in the center of the lesion. As a result of these changes, the blood supply to the periphery of the lesion becomes greatly diminished or even shut off; the central necrotic and suppurative areas become completely avascular.

* The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

Any attempt to treat such a lesion by the administration of any agent that has to reach the focus by way of the blood stream must by the very anatomy of the situation be doomed to failure.

It is apparent from these considerations that early administration of the medication is of the greatest importance insofar as the local lesion is concerned. The medication must reach the focus before the walling-off process, necrosis, and suppuration develop sufficiently to preclude the entry of the agent into the affected tissue.

A further consideration of utmost importance in the nature of the disease process encountered in infections of bones, joints, and their coverings is the existence of two major components, the systemic element and the local element. The nature of the latter has already been described. It is manifested clinically by localized throbbing pain, more disturbing at night; localized tenderness; heat; redness; disability; and, if allowed to go on improperly treated, swelling, suppuration, and sinus formation. The systemic element arises from the toxigenic and invasive characteristic of the causative microorganism. The toxigenic factors manifest themselves clinically by erythema, sustained elevation of temperature, persistently rapid and thready pulse, prostration, cold and clammy skin, vomiting, diarrhea, convulsions, and death, depending upon the severity of the toxemia. The invasive factors manifest themselves by chills, spiking temperature, and positive blood culture. Any combination and degree of severity of the toxic and invasive factors may be present in the systemic manifestations depending upon the severity and characteristics of the offending microorganisms. Antibiotic therapy, properly selected and utilized, is more readily effective in controlling the systemic manifestations of infections of bones, joints, and their coverings, because the therapeutic agent can readily come in intimate contact with the offending microorganisms in the blood stream and exert its influence by inhibiting them. One must, however, be aware of the fact that preformed toxins are not influenced by antibiotics. Therefore, to be effective, the drugs must be introduced before the toxins have become overwhelming.

In summation of these considerations, it becomes evident that, in general, oxytetracycline therapy, or for that matter any other form of therapy, be it serological, chemical, or antibiotic, is more effective against the systemic elements of the disease and less effective and sometimes ineffective against the local elements of the disease, depending upon the time of administration of the drug. One must therefore guard against being lulled into believing the therapeutic effects are successful because the systemic manifestations of the disease have subsided. The effects of treatment upon the local lesion must be judged by the response of the local lesion rather than the response of the systemic manifestations. Blind dependence upon drug therapy for the control of a local lesion that has become walled off and that presents areas of necrosis and suppuration will be met with failure. This has been demonstrated again and again by many observers. Oxytetracycline is no exception to this rule. Under such circumstances surgical intervention is imperative. Oxytetracycline or any other equally effective antibiotic when used in conjunction with the surgical approach plays a very important and effective role, the details of which will be presented later.

THE NATURE OF THE OFFENDING MICROORGANISM

By far the most common invader in infections of bones, joints, and their overlying tissues is the coagulase positive *Staphylococcus aureus*. The next most frequent invader, especially in the first few years of life, is the *Streptococcus*. The relatively rare invaders are the *Salmonella* group of organisms and the *Bacillus coli*. There are many strains of staphylococci and streptococci that, in addition to varying in their toxigenicity and invasiveness, vary also in their resistance to antibiotics. For example, in the early days of the use of penicillin, about 20 per cent of the staphylococcal strains were naturally resistant to the antibiotic and of the sensitive strains 20 per cent or more developed resistance during therapy. Now it has been shown that 90 per cent or more of the strains found in hospital populations may be resistant. At the time of introduction of oxytetracycline and the other broad-spectrum antibiotics, none of the staphylococcal strains were naturally resistant to these drugs. Since then, antibiotic resistance has been observed in 50 per cent or more of staphylococci cultured from infections. Many observers feel that natural resistance of the organism at the onset of infection is a much more serious problem than that which develops during therapy. Further it has been shown that resistance develops more readily to some antibiotics than to others. Streptomycin, for example, rapidly becomes ineffective in the presence of the staphylococcal organisms while the broad-spectrum antibiotics, such as oxytetracycline, are less likely to incur the development of resistance.

Further, many observers have noted that the mode of management of the lesions is a great factor in inducing resistance. Lesions that for one reason or another are left open induce resistance to the antibiotics more readily than lesions that are treated by primary closure and heal by primary intention. The latter method precludes the secondary invaders that often are resistant and may play a part in the prevention of healing.

In brief, one should realize that the coagulase positive *Staph. aureus* is the most common invader in infections of bones and joints. Compared to other pyogenic organisms, it is more likely to be resistant and is more likely to develop resistance to various antibiotics. The mode of therapy and the presence or absence of an open lesion play an important role in the effectiveness of the antibiotics in use. Oxytetracycline is no exception to this rule, though it is conceded that oxytetracycline and the other broad-spectrum antibiotics are up to the present time less affected by these considerations.

THE NATURE OF THE PATIENT'S RESPONSE

It is perhaps superfluous, but nevertheless important, to consider the patient's response to the invading microorganisms. It was pointed out that the most common microorganisms with which we are concerned in bone and joint infections are the staphylococci, which vary in their toxigenicity and invasiveness. During the acute phase of the lesion the toxic factor may play a very important role, since it may be so severe and overwhelming as to cause death. The patient's ability to develop an antitoxic response is most important, for antibiotics have no influence on preformed toxins. The effect of the antibiotics, and oxytetracycline is no exception

to the rule, is only indirect because, by their antibacterial influence, they prevent the formation of additional toxins. The preformed toxins must be destroyed by the patient's defensive responses. Fortunately, in the great majority of instances the patient is not overtaxed and is able to react adequately. This again demonstrates that the timing of the antibiotic is most important for its indirect aid in the defense against the toxic factors.

The response of the patient to the antibiotic being used is a deciding factor in its effectiveness. Many individuals respond with allergic manifestations and toxic reactions to certain antibiotics that are sufficiently severe to necessitate their discontinuance. Such responses of varying degrees are common in the use of penicillin and streptomycin as well as with other less frequently administered antibiotics. Oxytetracycline and other broad-spectrum antibiotics rarely if ever produce such manifestations. Gastric symptoms in the form of nausea, vomiting and—in the later stages—diarrhea are not at all uncommon, especially if large doses and prolonged administration are involved. This is only true of the oral use of these antibiotics. The nausea and vomiting are readily controlled by decreasing the dose or by the elimination of one or several doses if the situation warrants such action. The use of milk or other food at the time of administration of the drug is frequently effective. Dramamine if administered one-half hour before the oral dose of oxytetracycline is sometimes very effective. In those instances in which these simple measures are ineffective, administration of the drug intravenously or intramuscularly for several days will invariably relieve nausea and vomiting. Diarrhea may on rare occasions prove disconcerting. This is usually controlled by the common methods for the production of constipation or by the use of milk containing cultures of organisms commonly found in the intestinal tract. In retrospect, the author has seen relatively few and no severe untoward reactions to the use of oxytetracycline or the other broad-spectrum antibiotics.

THE NATURE AND INTENSITY OF THE USE OF THE ANTIBIOTIC

The choice of the antibiotic for use in any given case is most important. The considerations already mentioned point to the urgency of the early administration of antibiotic therapy in acute lesions, even before the organism can be isolated and tested for sensitivity. In view of this, one should utilize an antibiotic that has the broadest possible spectrum against those microorganisms most likely to be responsible and one that is least likely to induce allergic manifestations or toxic reactions. Oxytetracycline as one of the broad-spectrum antibiotics is therefore very suitable in infections of bones, joints, and their soft-tissue coverings, because it is effective against practically all the common organisms likely to be involved in these infection and the least likely to induce allergic or toxic manifestations. Furthermore it is important that the antibiotic be given in sufficient concentration to produce the desired antibacterial effect. Inadequate doses have been shown to develop resistant strains of organisms.

THE USE OF OXYTETRACYCLINE IN THE PREVENTION OF INFECTION

"An ounce of prevention is worth a pound of cure" is an adage that can be readily

translated into reality by the use of an appropriate antibiotic in those instances in which the development of an infection is a possibility. All operations carry the risk of a supervening infection, no matter how expert the surgeon or ideal the situation. This risk, though small in the aggregate, may be calamitous for the individual. It can be eliminated by the use of an appropriate antibiotic provided aseptic and atraumatic surgical techniques are followed. For more than a decade, the author has availed himself of the use of antibiotics in all surgical procedures and has encountered no postoperative infections in previously uninfected lesions.

In the early days of the antibiotic era, penicillin was the mainstay in the prevention of postoperative infections. Within recent years penicillin has been completely discarded by the author in favor of the broad-spectrum antibiotics for reasons indicated in the preceding discussion. The regimen now in use consists of the oral administration of 250 mg. of oxytetracycline every six hours for 24 hours prior to operation and the continuance of the same medication after the procedure for about 7 to 10 days. During the operative procedure the wound is repeatedly flushed with a solution of normal saline containing 0.5 mg. of intravenous oxytetracycline per ml. of diluent. Upon closure of the wound additional amounts of this solution are injected into the wound, which is then covered with a wet dressing of the same solution.

The rationale of this regimen is based on the erection of a barrier to local infection by the use of a high concentration of the antibiotic in the wound and by the erection of a barrier to the systemic spread of any local infection by the development of adequate concentration of the antibiotic in the blood stream. This regimen provides for ideal timing of the administration of the antibiotics to prevent the gaining of a "foothold" by any offending microorganism that might be introduced during the operation. The author urges that this or a similar routine be used in all operations on bones, joints, and their coverings, no matter how faint the possibility of infection may be. Certainly no untoward effects of any consequence have resulted from such use in an extensive experience with major surgical cases. The prophylactic use of the broad-spectrum antibiotic is "additional insurance" against postoperative infections, which has been most gratifying and reassuring.

THE USE OF OXYTETRACYCLINE IN ESTABLISHED INFECTIONS OF BONES AND JOINTS AND THEIR SOFT-TISSUE COVERINGS

As is evident from the earlier part of this presentation oxytetracycline therapy should be started as promptly as possible in acute lesions in doses of 500 mg. by mouth four times per day. If the patient is very ill, an initial dose of 500 mg. intravenously in 1000 ml. of saline and glucose or an intramuscular injection of oxytetracycline will produce an adequate blood level promptly. If within 24 to 48 hours or possibly 72 hours there is no evidence that the local lesion is being resolved, though the systemic manifestations are diminishing, one should approach the lesion surgically. The attack should consist of an incision along anatomic planes, thorough evacuation of the lesion, and closure of the lesion without drainage under antibiotic control. This involves the administration of 500 mg. of oxytetracycline intravenously in 1000 ml. of glucose in water and the local washing and flooding of the

lesion with a solution of normal saline containing 0.5 mg. of oxytetracycline per ml. of diluent. Upon recovery from the operative procedure, the administration of 500 mg. of oxytetracycline by mouth every six hours should be continued for a period of four weeks even though the temperature may be within normal limits. Should there be excessive nausea or vomiting with failure to retain the drug, the use of one or two intravenous infusions of 500 mg. of the drug in glucose in saline or sterile water for several days will relieve the gastric upsets. Intramuscular administration of 100 mg. of the drug four times per day will be similarly effective. The affected part is immobilized in a compression bandage of sheet wadding, flannel, and adhesive after a wet dressing of oxytetracycline solution has been applied. The wound is not disturbed until the tenth postoperative day or thereabouts, when the wound will be found to be healed by primary intention and the sutures may be removed. The part should thereafter be immobilized again in a compression bandage for a total of three to four weeks.

The administration of antibiotics including oxytetracycline in chronic infections of bones and joints without operation is highly inadvisable, is ineffective, and should be condemned. As previously indicated in this presentation, these lesions are walled off and therefore are not influenced by the systemic administration of the therapeutic agent. Similarly, these lesions are not influenced by the local application of the drug because it cannot reach the entire lesion if the focus is closed. The administration of oxytetracycline or any other antibiotic under such circumstances produces an inadequate concentration of the agent in the chronic focus with the result that the microorganism develops resistance to the antibiotic. Then when a surgical procedure is eventually undertaken, the previously used antibiotics may be ineffective.

The use of oxytetracycline in chronic infections subjected to operation is similar to its use in acute infections. Thus, 500 mg. of the antibiotic are administered orally every six hours for 24 hours prior to the operative procedure. During the course of the operation, 500 mg. are administered intravenously in 100 ml. of diluent and the wound is thoroughly washed and flooded with a solution of normal saline containing 0.5 mg. of the antibiotic per ml. of diluent. The surgical procedure should consist of a thorough excision of the bony and soft-tissue foci including all sinuses followed by closure of the wound without drainage. The wound or wounds are covered with dressings wet with the antibiotic solution and immobilized in a compression dressing. On recovery from the operation the antibiotic is administered, 500 mg. by mouth, four times per day for approximately four weeks. With the use of this technique the author has been able to obtain 80 to 90 per cent primary closures with an insignificant rate of recurrences in a period of observation ranging up to 10 years.

THE USE OF OXYTETRACYCLINE IN COMPOUND FRACTURES, DISLOCATIONS, AND WOUNDS OF THE SOFT TISSUES

In view of the very gratifying results obtained following the use of the antibiotic as a prophylactic agent and its use in infected lesions of bones and joints, similarly gratifying results follow the use of oxytetracycline in the treatment of compound

fractures, compound dislocations, and wounds of the soft tissues. With the use of the antibiotic the urgency of operation is reduced and the "golden period," during which intervention is safe, is extended. The regimen is essentially similar to that used in chronic infections of bones and joints. If operative interference should be delayed for one reason or another, the oral administration of 500 mg. of oxytetracycline by mouth every six hours should be started immediately. During the operative procedure, an intravenous infusion containing 500 mg. of the drug should be administered and the lesion should be washed and flooded with the antibiotic solution. Upon recovery from the procedure, 500 mg. of the antibiotic should be administered orally four times per day for 7 to 10 days. It should be emphasized that early operative intervention and thorough excision of devitalized tissues and the removal of foreign bodies are most essential for the prevention of a supervening infection. Furthermore, the earlier the intervention the safer will be the use of metallic substances for the fixation of bones. In the presence of a fully developed infection, metallic fixation is contraindicated. Primary closure should, however, be performed after thorough removal of diseased and devitalized tissues and foreign bodies. Other means than internal metallic fixation should be utilized.

OXYTETRACYCLINE AS CONTRASTED WITH OTHER BROAD-SPECTRUM ANTIBIOTICS

Determination of sensitivity on the part of the microorganisms to the various broad-spectrum antibiotics have shown that resistance to one antibiotic does not always indicate resistance to other antibiotics of the same group. It is therefore incumbent to test for sensitivity whenever feasible to determine which of the broad-spectrum antibiotics should be administered. The author has used oxytetracycline, chlortetracycline,* carbomycin,† and tetracycline* with equal effectiveness depending upon the sensitivities encountered. He has further noticed that nausea and vomiting may be induced by one of these antibiotics and not by another. The reaction of the patient is therefore another criterion that determines the choice of the drug. The regimens already described are essentially similar to that used with each of these drugs except for dosage.

CONCLUSION

This presentation deals with the use of the broad-spectrum antibiotics, oxytetracycline in particular, in the prophylaxis and treatment of infections of bones, joints, and their coverings. The reasons that the use of these drugs may be ineffectual have been discussed in some detail so they may be avoided. Operative treatment is essential in many instances. The combination of antibiotic therapy and operative treatment will in these instances give the best results. Inadequate operative treatment cannot be rectified by antibiotic therapy. On the other hand, inadequate antibiotic therapy cannot be rectified by operative treatment.

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* The trade names of Lederle Laboratories Division, American Cyanamid Co., for chlortetracycline and tetracycline are Aureomycin and Achromycin.

† The trade name of Chas. Pfizer & Co. for carbomycin is Magnamycin.

Oxytetracycline as an Adjunct to Surgical Therapy in Established Peritonitis and Peritoneal Contamination

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Antibiotics, far more than chemotherapeutic agents, have proved their value as bacteriostatic and bacteriocidal agents. Their use constitutes a major factor in the steady decline in the death rate from peritonitis as reported by numerous investigators throughout the country.[1–3] Penicillin in varying dosages and streptomycin alone or in combination with penicillin, despite their proved worth, have failed on occasion to prevent deaths from bacterial invasion. Broad-spectrum antibiotics in our hands significantly altered our mortality expectancy to the point where death from uncontrolled peritonitis in acute surgical emergencies has been reduced to negligible proportions.[4–7] However, there still occurs occasionally a fatality owing to uncontrolled bacterial infection in the peritoneal cavity.

The wide and remarkable antimicrobial activity of oxytetracycline has been the subject of many recent papers.[8–23] Both animal experiments and clinical trials indicate that this antibiotic is effective in the treatment of infections of the peritoneal cavity.[24–26] On this basis and the logical assumption that an agent with a wide antibacterial range would prove efficacious in reducing the mortality from peritoneal infection, oxytetracycline* was selected for investigation.

CASE MATERIAL

In Harlem Hospital, a municipal institution situated in a densely populated section of the city, the ward patients frequently present a low nutritional status. These patients, because of economic factors, postpone seeking medical assistance and almost invariably the disease process is well advanced on admission to the hospital.

The 114 cases chosen for this study fall into two major groups: (1) established peritonitis, either localized or diffuse, of which there were 88 cases; and (2) peritoneal contamination, which includes 26 cases. In the former group there was antecedent organic pathology with bacterial invasion. In the latter group, comprised largely of traumatic cases, this did not hold true. The distinction is thus drawn so as to define clearly the bacterial status of the peritoneum at the time of operation, for it establishes a specific group of cases that may possibly develop a suppurative peritonitis. In table I we summarize our experience with the 88 cases of peritonitis in which oxytetracycline was used as an adjunct to surgery. Table II presents data

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* The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

TABLE I

Analysis of 88 Cases of Peritonitis in Which Oxytetracycline Was Used as an Adjunct to Surgery

Cause of Peritonitis	Number Cases	Type of Peritonitis		Operative Procedure	Number Deaths	Mortality Rate, %
		Generalized	Localized			
Appendicitis	66	20	46	Appendectomy 61*	2†	3
Perforated gastroduodenal ulcer	20	20		Simple closure	1‡	5
Ruptured carcinoma of stomach	1	1		Simple closure	1§	
Ruptured diverticulum of cecum	1	1		Excision of diverticulum & appendectomy		
TOTAL	88	42	46		4	

* Incision and drainage of appendiceal abscesses performed in 5 cases.

† Cause of death was carcinoma of stomach with carcinomatosis, uncontrolled infection and wound dehiscence.

‡ Cause of death was peritonitis of more than 72 hours' duration. Patient died postoperatively.

§ Cause of death was carcinoma of the stomach with carcinomatosis.

on the management of cases of peritoneal contamination in which oxytetracycline was used prophylactically in conjunction with various surgical procedures.

TABLE II

Analysis of 26 Cases of Peritoneal Contamination in Which Oxytetracycline Was Used as an Adjunct to Surgical Treatment

Pathology	Number Cases	Type of Operation	Number Deaths
Traumatic Cases			
Stab wound of abdomen with or without visceral herniation	15	Celiotomy	0
Stab wound of abdomen with small bowel laceration	4	Celiotomy with closure of intestine	0
Stab wound of abdomen with large bowel involvement	2	Celiotomy with closure of colon	0
Gunshot wound of abdomen	2	Left nephrectomy, closure of lacerations of stomach	0
Emergency Bowel Resections			
Mesenteric thrombosis	1	Resection of small bowel	0
Strangulated hernia	1	Resection of ileum	0
Prolapsed ileum through perforated uterus	1	Hysterectomy & resection of ileum	0
TOTAL	26		0

THERAPEUTIC PROCEDURES USED

Surgery was performed chiefly by the resident staff under the supervision of visiting staff members. The routine management of these cases was altered only in that once the decision to operate was made, the patient received oxytetracycline intravenously and the administration of the antibiotic was continued during the postoperative period. At operation specimens of peritoneal fluid were taken for culture and only those cases in which bacterial growth was demonstrated were followed under this study. In table III we record the results of in vitro tests on the sensitivity to oxytetracycline of the microbial strains isolated from these patients.

TABLE III

Sensitivities to Oxytetracycline of Microorganisms Recovered From 88 Cases of Peritonitis

Organism	Strains Inhibited by Oxytetracycline		Total Strains Isolated	% Inhibited by	
	0 to 10 μg./ml.	More than 10 μg./ml.		0 to 10 μg./ml.	More than 10 μg./ml.
Micrococcus pyogenes var. *aureus* (A)	9	8	17		
Micrococcus pyogenes var. *aureus* (B)	3	1	4		
Micrococcus pyogenes var. *albus* (A)	2	3	5		
Micrococcus pyogenes var. *albus* (B)	6	2	8	58.82	41.18
Gaffkya tetragena	0	1	1		
Beta hemolytic streptococci (Group A)	2	0	2		
Alpha hemolytic streptococci (Group D)	31	2	33		
Nonhemolytic streptococci (Group D)	1	0	1	94.44	5.56
Species of clostridia	3	0	3		
Klebsiella pneumoniae type "A"	2	0	2		
Diphtheroids	15	0	15		
Bacillus subtilis	5	0	5		
Yeast	0	1	1		
Neisseria catarrhalis	2	0	2		
Chromobacteria	4	0	4		
Escherichia coli	44	7	51	86.27	13.73
Aerobacter aerogenes	3	0	3		
Paracolon bacillus	5	4	9		
Bacillus proteus	0	6	6		
Pseudomonas aeruginosa	3	1	4		
Bacteroids	2	1	3		
Anerobic streptococci	2	0	2		
	144	37	181	79.56	20.44

Oxytetracycline hydrochloride was employed intravenously in doses of 500 mg. twice daily. When an oral regimen was used, the dosage was 1 or 2 Gm. daily. The 1 Gm. schedule gave as good results as did the 2 Gm. dosage and was accompanied by fewer side reactions. In this study intraperitoneal administration of the

antibiotic was not employed.[27] Children received proportionately less of the antibiotic.

Side reactions to intravenous therapy were few and consisted chiefly of localized thrombosis of the vein after repeated or prolonged infusions. This is an annoying condition, but in no instance was any permanent deleterious effect suffered by the patient. In the series of patients with peritonitis who were receiving oral medication, 6 per cent were noted as experiencing nausea, vomiting, bulky stools, or diarrhea. In no case was it necessary to withdraw the antibiotic because of these symptoms.

ESTABLISHED PERITONITIS

Appendiceal Peritonitis. During the period of this study, 66 cases of appendiceal peritonitis, either local or generalized, were treated with oxytetracycline in conjunction with surgery. Appendectomies were performed initially on 61 patients and in 5 cases incision and drainage of the appendiceal abscesses was done. Appendectomies were subsequently performed in the latter cases as elective procedures. In order to complete the picture, 3 of 4 additional cases coming to the service during the course of this study are not included in the tabulation because these patients had received other antibiotics prior to surgery and the fourth died before an antibiotic was administered.

The over-all mortality for the 70 cases of appendiceal peritonitis admitted during this period was 4.3 per cent. The mortality in the cases treated by operation and oxytetracycline was 3 per cent. This figure compares favorably with the results obtained by us in a similar series in which chlortetracycline* was employed and is far superior to our experience before the advent of the broad-spectrum antibiotics.[27] Of the two deaths, one patient had had a gastrectomy, had been severely ill for three days, and at operation was found also to have widespread carcinomatosis. The other patient was a diabetic whose diabetes was difficult to control and who was also severely ill three days prior to operation.

Details of the 2 deaths in this group follow. It is apparent that in the second case uncontrolled infection was a causative factor in the death.

CASE HISTORY. (No. 52-8596) G. K., a 52 year old man was admitted to Harlem Hospital on May 16, 1952, with the chief complaint of abdominal pain, associated with anorexia and loss of weight. The pain in the abdomen had been severe during the preceding three days. One year previously the patient had a gastrectomy for carcinoma of the stomach.

The physical examination was essentially negative except for a well-healed left upper abdominal scar. There was tenderness and spasm in the left mid-quadrant.

Laboratory studies established the existence of secondary anemia and a white blood cell count of 16,700, with 85 per cent segmented cells.

On June 9, 1952, it was decided to operate upon the patient for intestinal obstruction. At operation an appendiceal abscess was found with numerous adhesions of the bowel to the inflammatory area. There was widespread carcinomatosis. The appendix was removed, the abscess cavity drained, and the wound closed in layers.

* The trade name of Lederle Laboratories Division, American Cyanamid Co., for chlortetracycline is Aureomycin.

Postoperatively oxytetracycline, 500 mg. intravenously, was administered twice daily and the patient appeared to improve. The abdomen was flat and nontender. On June 14, 1952, the patient died suddenly.

Case History. (No. 52-19908) F. L., a 42 year old man, was admitted to Harlem Hospital on November 26, 1952, with a history of an irreducible right hernia for the past 12 years. Two days before admission he developed a dragging pain in the right inguinal region. He had diabetes and hypertension.

Physical examination revealed an irreducible right inguinal hernia with tenderness and spasm in the right lower quadrant.

Urinalysis showed albumin, three plus sugar, and acetone. The red and white blood cell counts were normal.

The day following admission the abdomen became distended and the patient vomited. At operation generalized peritonitis with a ruptured gangrenous appendix was found. An appendectomy was performed.

Postoperatively oxytetracycline was administered. The diabetes was difficult to control. The abdomen continued distended. On the eleventh postoperative day the patient suffered a wound dehiscence. The wound was resutured. He developed patchy areas of infiltration in both lung fields. The temperature curve continued to spike. The downhill course continued and the patient died on the twenty-fifth postoperative day.

We believe that in this case the infection was not at any time brought under control. Culture of the abdominal fluid at the time of operation showed *Escherichia coli* and alpha streptococcus hemolyticus.

In the cases of appendiceal peritonitis, oxytetracycline was given intravenously for an average of two days. This was to insure an adequate intake of the antibiotic and also to avoid the risk of loss of the drug by vomiting. It was observed that children required fewer intravenous doses than did adults. Oral oxytetracycline was administered for an average of seven days. It was found that the 1 Gm. daily dose was adequate and gave rise to fewer side reactions than the 2 Gm. dose. In no case was it necessary to withdraw the antibiotic because of side reactions. The postoperative course was especially gratifying in these cases. Within 36 hours the patient's condition changed from that of an acutely ill person to the recovery stage. The recovery of the 12 children in this series was unattended by any complications.

Twenty of the adults had associated diseases in the following order of frequency: hypertension, 15 cases; diabetes, 4 cases; arteriosclerotic heart disease, 3 cases; tuberculous peritonitis, 1 case.

Complications of surgery in the adult patients were as follows: wound infection, 7 cases; pneumonia, 3 cases; cardiac failure, 1 case; intestinal obstruction, requiring secondary surgery, 1 case; thrombophlebitis (saphenous vein of left leg), 1 case; wound dehiscence, 1 case.

Peritonitis from Perforation of Gastroduodenal Ulcer. We had the opportunity to study 21 cases of peritonitis from perforated gastroduodenal ulcers. Twenty cases were treated by operation and oxytetracycline. One patient was treated with a combination of penicillin and oxytetracycline in addition to surgery. There were 2 deaths. Therefore, the over-all mortality for this group was 9.5 per cent. The mortality for the cases treated with oxytetracycline as an adjunct to surgery was 5 per cent.

Here again the postoperative course of these patients was remarkable. They received intravenous oxytetracycline for an average of three days and oral therapy for an average of eight days. Within 36 hours the patients were comfortable and thereafter their recovery was uninterrupted. In the group of 20 cases, the con-

valescence was complicated by: minor wound infection, 3 cases; pneumonia, 2 cases; partial intestinal obstruction, 1 case; pelvic abscess with spontaneous resolution, 1 case.

Following is a brief history of the 1 death in the group of perforated gastroduodenal ulcers treated with oxytetracycline in conjunction with surgery. It is obvious that in this case the delay in surgery resulted in irreversible infection.

CASE HISTORY. (No. 53-4038) M. C., a 39 year old woman was admitted to the Medical Service on March 3, 1954, complaining of abdominal pain of six hours' duration. On physical examination the abdomen was found to be tender and distended. Air under the diaphragm was demonstrated roentgenographically.

Surgery was proposed but refused by the patient. Gastric suction and oxytetracycline therapy were instituted. The patient went into shock on March 5. She then consented to operation.

The operation revealed a perforated peptic ulcer, but the patient died on the table. Pus from the peritoneal cavity cultured alpha streptococci and *Aerobacter aerogenes*.

Other Types of Peritonitis. Two other cases of established peritonitis were treated under this study. Infection in one case came from a carcinoma of the stomach that perforated, and the patient died of carcinoma one month after surgery. However, both these patients made a complete recovery from the peritonitis.

SERIES OF PATIENTS WITH PERITONEAL CONTAMINATION

In the final category of peritoneal contamination, infection is only one of the many important factors that must be controlled. Multiple injuries and delay in operation often are not the total actual difficulties encountered by the surgeon. Mortality rates therefore vary and there is, unfortunately, no true method for comparing cases of this type. By a careful study of each death, we can often determine whether uncontrolled infection played a dominant role in the loss.

In table II our experience in cases of peritoneal contamination is summarized. It was fortuitous that there were no deaths in this group, but this may have been because the series was relatively small. However, in many of these cases peritonitis as a complication would have been a foregone conclusion without antibiotic therapy. Oxytetracycline therefore was a significant factor in the prevention of peritonitis in those cases.

The postoperative course of these 26 patients was eminently satisfactory. Intravenous therapy was required for an average of four days and oral treatment for seven days. In spite of the gravity of the illness and the magnitude of the emergency operation, only 1 patient had a stormy postoperative course.

This patient, a 29 year old man, sustained a stab wound of the abdomen with transection of the jejunum. The laceration was repaired at operation, but the postoperative course was complicated by a bout of partial intestinal obstruction, which was alleviated by conservative therapy. At the time of discharge two weeks later he was asymptomatic.

BACTERIOLOGIC STUDIES

Microorganisms isolated from the surgical cases in this study were subjected to twofold dilutions of oxytetracycline in tubes. The minimal inhibitory concentration was recorded after a 24-hour incubation and the end point was read macro-

scopically. In table II we report the sensitivity to oxytetracycline of 181 strains of organisms isolated from 88 cases of peritonitis.

It is interesting to note that the growth of at least 79.56 per cent of the isolated microorganisms was inhibited by concentrations of the antibiotic up to 10 μg./ml., while 20.44 per cent were inhibited by concentrations greater than 10 μg./ml. From a list of the various *Micrococcus pyogenes* strains compiled together, it will be noted that 58.22 per cent were sensitive to concentrations from 0 to 10 μg./ml., while the growth of 41.18 per cent was inhibited by concentrations of more than 10 μg./ml. By combining all aerobic growing streptococci, it was found that 94.4 per cent were sensitive to the antibiotic in the range from 0 to 10 μg./ml., while 5.56 per cent were inhibited by concentrations greater than 10 μg./ml. A total of 51 strains of *E. coli* were isolated, of which 86.27 per cent were inhibited by 0 to 10 μg./ml., and 13.73 per cent were sensitive only to concentrations greater than 10 μg./ml. There were too few strains of various other gram-positive and gram-negative organisms to justify any definite conclusions as to their sensitivity to the antibiotic.

In comparing the results of the strains of microorganisms tested in vitro to oxytetracycline with the antibiotic levels in blood from the patients under treatment, it is encouraging to note that 70.56 per cent of the strains were inhibited by concentrations well within the blood levels achieved in the in vivo use of the antibiotic. However, gram-negative organisms, such as *Bacillus proteus*, appear to be completely refractory to oxytetracycline.

The organisms isolated from the 3 fatal cases of peritonitis were as follows: two strains of *E. coli*, two strains of alpha hemolyticus streptococci, and one strain of *A. aerogenes*. With the exception of the *A. aerogenes*, all the organisms were inhibited by 10 μg./ml. of oxytetracycline. It is obvious that now, more than ever before, exact studies of the bacteriology of infections are necessary in order that the appropriate antibiotic or antibiotics be employed.

SUMMARY

Experimental and clinical evidence indicated the effectiveness of oxytetracycline as an adjunct in the surgical treatment of severe peritoneal infections.

In 88 cases of peritonitis treated by operation and with oxytetracycline as the antibiotic, 85 were successful. Of the 3 deaths, one was a patient with widespread carcinomatosis, one was a hypertensive diabetic whose diabetes was difficult to control and whose infection was not brought under control, and one was a patient with gastroduodenal perforation who refused operation for two days and who died during the operation, which could be undertaken only after the patient had an episode of shock and had given operative consent.

In 26 cases of peritoneal contamination there were no deaths. These results compare favorably with those obtained when chlortetracycline was employed and are decidedly lower than the mortality rates secured earlier in our experience.[16]

The dosage schedule found most satisfactory was 500 mg. of oxytetracycline intravenously twice daily and a similar dose administered orally when postoperative

gastrointestinal decompression could be discontinued. The dosage administered to children was proportionately smaller.

This dosage schedule was confirmed by findings as to serum and peritoneal fluid levels of oxytetracycline, in vitro sensitivity of various microorganisms to oxytetracycline, and by the clinical results.

Side reactions, when they occurred, were minimal in all cases, and in no instance was it necessary to withdraw the antibiotic because of such manifestations.

Despite severe associated disease, multiple injuries, and major surgical procedures, the postoperative course of these patients was benign and complications of surgery, such as pneumonia, wound infections, and pelvic abscesses, required no additional antibiotic therapy.

The bacteriologic findings are listed in detail. The mixed flora found in the peritoneal fluid constitute organisms that generally are quite sensitive to oxytetracycline. It is now more than evident that bacteriologic studies should be made at the time of operation so that the appropriate antibiotic or antibiotics may be used in the treatment of the patient.

CONCLUSION

That oxytetracycline has wide applicability of great value as an adjunct in the surgical management of peritonitis and peritoneal contamination is beyond question.

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Oxytetracycline in Obstetric Infections

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Types of Obstetric Infection. Infection occurring in obstetric patients falls into three general categories: the puerperal, the mammary, and the incidental.

Obstetric or puerperal infection proper either (1) arises in the genital tract or (2) settles in the genital tract in association with pregnancy, labor, or the puerperium. In group (1), infection of the genital tract, the infection ascends from the vagina and may spread by direct invasion through the tissue or through the blood stream or lymphatics. In group (2) the infection localizes in or extends into the uterus from an infection elsewhere in the body. For example, an appendical abscess or some other infection may gravitate to or attach itself to the uterine wall. Another illustration might be an infection secondary to perforation of the bowel or diverticulitis. The infection spreads through the uterine wall, thereby causing trouble. Spread by means of the blood stream from other sources to the uterus is possible but not common. This type of dissemination results from bacteremia.

Most puerperal infections are due to endometritis. In the modern well-run maternity service, the great majority of these infections are endogenous; that is, the organisms have invaded upward from the vagina into the uterine cavity. The exogenous organisms can be largely excluded by good technique. Even so, contamination may occur in rare instances.

Puerperal infections include endometritis, parametritis, peritonitis, and bacteremia. Bacteria may be disseminated by the vascular system throughout the body and frequently cause localized lesions in one or more sites. Frequently an overwhelming number lodge in multiple sites. Some bacteria may be eliminated through the urinary tract. Many microorganisms are destroyed by the body's protective mechanisms. The nature of local lesions will vary according to the characteristics of the specific invader and the response of the tissue attacked. Features of the inflammation may include hemolysis, cellulitis, suppuration, and so on. There is good evidence that many bacteria enter the blood or lymphatic streams in apparently normal individuals without producing an inflammatory reaction in the body. In these instances the organisms are presumably of such type or number as to be controlled by the patient's natural mechanisms or resistance and immunity.

Another type of infection that occurs occasionally in postpartum patients is infection in an episiotomy or abdominal wound, incidental to the delivery. This is of minor importance usually in comparison to the problem of endometrial infection.

With the onset of labor bacterial invasion of the uterine cavity begins. The bacteria increase reaches the greatest number about the third to eighth postpartum day and remain in gradually decreasing numbers in the uterine cavity until the placental site is healed. The placental site is thought usually to heal in six to eight weeks. A placental site may however be still unhealed after three months, particularly if there is retention of placental tissue.[5] The placental site becomes necrotic immediately following delivery and the vessels under the site are thrombosed. The healing of the surface proceeds from the edge toward the center. Occasionally there is excessive bleeding associated with the slough.

The intrauterine bacteria are of the types ordinarily present in the vagina. Their number varies somewhat depending upon the general health and resistance of the patient. No one has shown that the puerperal uterine cavity can be kept bacteria-free during or after labor by the use of drugs. The species of bacteria present can be altered but they cannot be completely eliminated by the use of antibiotics. While certain strains may be decreased, frequently others are actually increased appreciably. This was demonstrated by Hesseltine, Bustamante, and Loth[3] who compared the results in groups of patients receiving chlortetracycline,* chloramphenicol,† penicillin, streptomycin, and oxytetracycline‡ with a group of patients serving as controls. The number of *Staphylococcus albus* in the uterine cavity was found to be appreciably increased after the administration of chlortetracycline and chloramphenicol and oxytetracycline.[3] The number of *Staphylococcus aureus* increased most after the administration of penicillin and oxytetracycline. This finding was contrary to expectations. Perhaps the growth of certain strains was enhanced by lack of competition with other bacteria or by stimulation of those present. The use of penicillin resulted in an increase in the growth of *Escherichia coli*. The increase may have been favored by penicillin or, more likely, the organisms thrived because of the reduction of diphtheroids, anaerobic streptococci, and bacteroids, which were suppressed. Either contention could prove to be valid. *E. coli* growth was reduced by chloramphenicol, streptomycin, and oxytetracycline. The growth of *Proteus vulgaris* was favored by all five antibiotics while diphtheroids were retarded by the same five antibiotics. The anaerobic streptococci were reduced in number by all but streptomycin. The same pattern was followed by bacteroids.

It is interesting that Leberman, Smith, and Morton[8] found that oxytetracycline inhibited the growth of pleuropneumonia-like organisms under certain conditions. They felt that it is the drug of choice for this strain. In the study by Hesseltine et al, these bacteria were not isolated. According to Bliss, Warth, and Chandler,[1] clostridia were inhibited by penicillin, oxytetracycline, and chlortetracycline.

Textbooks and clinicians have contended in the past that the normal uninvaded, nongravid uterine cavity is a sterile field. Sampling studies in our laboratory have

*The trade name of Lederle Laboratories Division, American Cyanamid Co., for chlortetracycline is Aureomycin.

† The trade name of Parke, Davis & Co. for chloramphenicol is Chloromycetin.

‡The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

demonstrated that, when sufficient material is obtained by proper techniques, one will find organisms in moderate frequency in the presumably normal uterine cavity.[9] Hence it seems that our older concepts concerning the bacterial flora of the lower genital tract and uterus must be re-evaluated in several particulars. One may certainly expect to find organisms after curettement or other invasion of the uterine cavity. In obstetric practice it is recognized that the so-called "sterile vaginal examination" is actually a physical means of carrying vaginal organisms through the dilated cervix into the lower uterine cavity. Any pelvic examination should be gentle and without damage to tissue.

THE PROBLEM OF RUPTURED MEMBRANES

Artificially rupturing membranes initiates invasion of bacteria with the risk of more rapid growth of bacteria in the uterine cavity. On the other hand, when the membranes rupture spontaneously and the fetus is in a longitudinal presentation, bacteria apparently fail to ascend until after digital examination or labor ensues. At one time it was considered practically mandatory that the patient be delivered reasonably soon after the bag of waters ruptured. In retrospect it now seems that the efforts to induce labor may have been an insulting factor. When the body of the fetus is in the transverse position, infection may occur during a poor or faulty labor. At the Chicago Lying-In Hospital it is the practice not to use antibiotics when the membranes rupture spontaneously. Most patients whose membranes have ruptured will go into labor within a few days. Curiously the Braxton Hicks contractions do not predispose to bacterial invasion. But once labor ensues the invasion begins. Whether these bacteria serve any useful purpose is questionable. Possibly they may help to digest the necrotic tissue of the placental site and thus aid in the restoration of the normal uterine cavity.

TREATMENT OF ENDOMETRITIS

Whenever there is any possibility that a patient may have endometritis, she should be treated on this basis. The treatment of endometritis is based on rest for the infected organ. Oxytocic drugs are not recommended, since they may not produce a response and, moreover, any infected organ should not be stimulated. The procedure of taking intrauterine cultures insures that drainage from the uterus will be promoted.

The choice of antibiotic depends on the severity of the case. The mild case usually responds to penicillin. It should be given as the procaine or slowly absorbing type and in a dosage of 600,000 units twice daily. More severely infected patients should have 200,000 units of crystalline penicillin and 600,000 units of procaine penicillin at once. Thereafter 600,000 units twice daily of the slowly absorbing type. Streptomycin in 1 Gm. doses four times daily for not more than seven and preferably five days aids in wider coverage of the bacterial spectrum.

Patients who have had penicillin on previous occasions may do better on 0.5 Gm. of erythromycin four times daily. If there is unsatisfactory progress, oxytetracycline, 0.5 Gm. four times daily, should be substituted for streptomycin after five to

seven days. Oxytetracycline does have a broad coverage. Used with penicillin or erythromycin, oxytetracycline serves well in the treatment of endometritis. The principal intolerance encountered in the oxytetracycline study by Caldwell et al[2] was nausea.

DIAGNOSIS AND TREATMENT OF PELVIC PERITONITIS

The diagnosis of puerperal peritonitis is difficult to make because the usual typical findings, such as distention, tenderness, and rebound reaction, may be absent at the beginning. In the early stage there may be little or no true evidence of peritonitis. Only about 70 per cent of these patients will show evidence of abdominal distention. A slight increase in the white count occurs after delivery but a pronounced change should be viewed with concern. A smaller percentage will have vomiting. It is possible for a puerperal patient dying from generalized peritonitis to eat and even retain fluids given orally. Whenever there is the slightest diagnostic indication of peritonitis, one should institute appropriate treatment immediately. This therapy includes parenteral fluids in balanced amounts with the vitamins (ascorbic acid, thiamine, and riboflavin) and blood for both red cell replacement and protein intake. Although important, blood should be given only on direct indication, for there are potentially serious and fatal complications associated with blood transfusions. Gastric siphonage may need to be instituted early. Full coverage with antibiotics by intramuscular and intravenous routes should be started early in ample amounts.

INCIDENTAL INFECTIONS IN PREGNANCY AND POSTPREGNANCY

Incidental, nonobstetric infections must be expected in pregnant women about as often as in the nonpregnant. Of these, infections of the pelvis, of the kidney and the upper respiratory tract are most frequent. However, any and every type of infection, such as cholecystitis, cystitis, appendicitis, and the acute contagious diseases, is a potential menace.

Any intrapartum or postpartum patient with a febrile course must at first be assumed to have puerperal infection until specific and concrete evidence to the contrary can be presented. The mere presence of white cells in the urine is not proof that a urinary tract infection exists. It has been pointed out that a large number of women will have some pyuria as a result of trauma to the bladder walls in association with labor and delivery. During labor the bladder is (1) pulled up into the abdomen, (2) compressed by the advancing head, or (3) forced downward in advance of the presenting part. Frequently the bladder is so traumatized that it cannot continue to function normally. Thus overdistention causes breaks in the mucosa of the bladder; this is followed frequently by cystitis.

The typical pyelitis has the usual symptom complex, which includes the sudden onset of a pronounced elevation of temperature. Unless one can find characteristic evidence of pyelitis per se one should be reluctant to accept the diagnosis of urinary tract infection as the cause of the fever. The white count may vary from normal to a moderately pronounced leukocytosis (8,000 to 20,000). As a rule there is definite kidney tenderness.

King et al[7] have reported on the good therapeutic effect of oxytetracycline for urinary tract infections. Usually 0.5 Gm. of oxytetracycline four times daily by mouth will yield a prompt response.

To make a diagnosis of an upper respiratory infection requires more than trivial evidence. The responsibility for this and for the choice of therapy are problems for the internist.

REPORT OF ILLUSTRATIVE CASES

The effectiveness of oxytetracycline in a patient with endometritis is shown in figure 1. The febrile course was rather sudden in onset beginning four days after

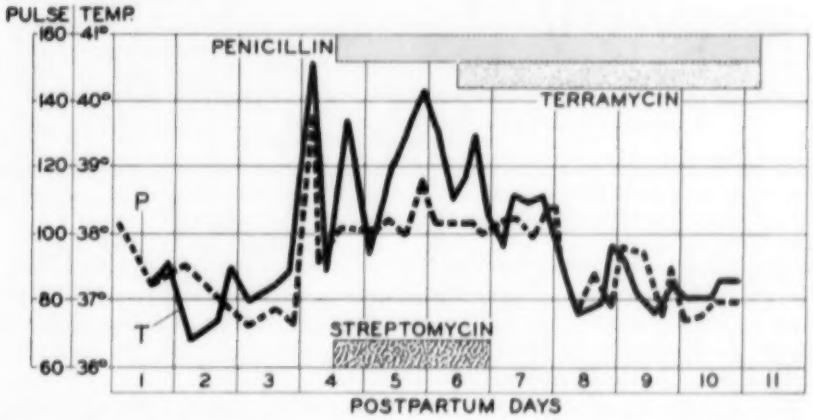

FIG. 1. Antibiotic therapy in a patient with puerperal sepsis. After an initial dose of 200,000 units of crystalline penicillin, 600,000 units of procaine penicillin were given twice a day. Streptomycin was given in a dosage of 1 Gm. four times a day on the first through the third day of treatment. At this time because there was no clinical improvement, the streptomycin was stopped and oxytetracycline was started intravenously in a dosage of 1 Gm. twice a day. The patient improved and two days later the dosage of oxytetracycline was changed to 0.5 Gm. four times a day by mouth.

delivery. Uterine culture revealed *E. coli*, alpha streptococcus, and *Staphylococcus albus*. Penicillin was given in dosage of 1,200,000 units daily and streptomycin in a dosage of 4 Gm. daily. By the sixth postpartum day (third day of treatment) there was no obvious evidence of clinical improvement. Streptomycin was discontinued on this day and oxytetracycline instituted. The latter was given in 2 Gm. amounts daily (1 Gm. twice daily when given intravenously in parenteral fluids and 0.5 Gm. four times daily when given orally). The improvement was prompt. The temperature, which had been gradually on the incline, receded after oxytetracycline was added. In this instance oxytetracycline was probably the most significant of the three antibiotics.

Figure 2 illustrates the course of a patient in whom a Meckel's diverticulum became involved in an intussusception on the patient's second postpartum day. The condition was corrected by operation on this day. The course was rather stormy until

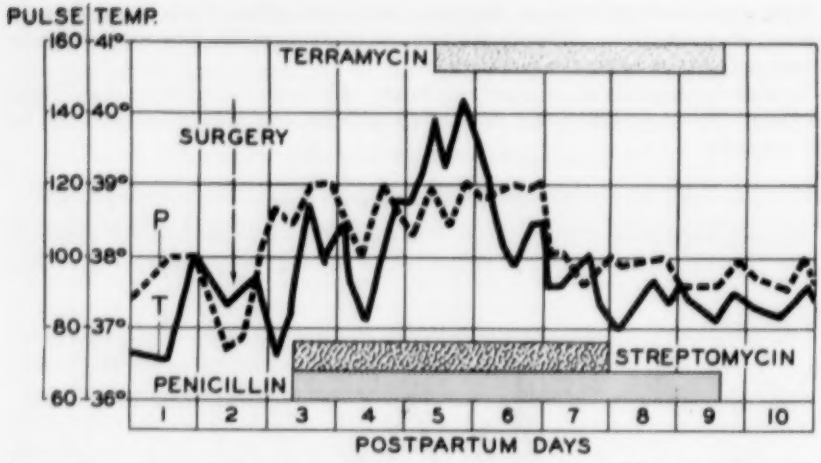

Fig. 2. Course of a patient operated upon for an intussusception on the second day after delivery. After operation she was given 1,200,000 units of penicillin and 2 Gm. of streptomycin daily. She continued to have a stormy course until oxytetracycline was started on the third postoperative day.

the fifth day when oxytetracycline was instituted. Up to this time 2 Gm. of streptomycin and 1,200,000 units of penicillin had been given daily. Following the introduction of oxytetracycline the clinical course improved rapidly as indicated by the graph. Administration of oxytetracycline was continued up until the ninth day when antibiotics were discontinued.

Pyelitis occurs infrequently in the postpartum obstetric patient. Figures 3 and 4 reveal the favorable response to oxytetracycline in two such infected patients. Figure 3 indicates the course in one from the sixteenth to the twenty-third postpartum day.

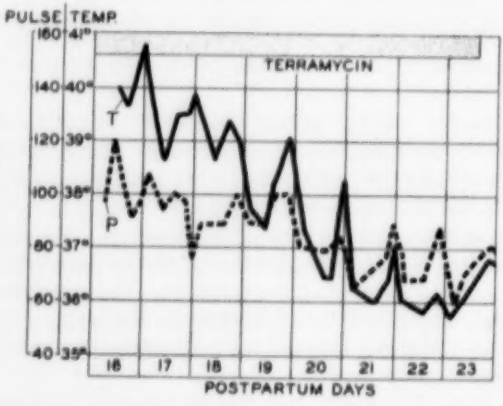

Fig. 3. Patient with pyelitis admitted 16 days after delivery. She had been ill for 36 hours prior to admission. Oxytetracycline was started on admission in a dosage of 0.5 Gm. four times daily.

The drug was given in a dosage of 0.5 Gm. four times daily. The response may seem gradual but this patient was ill approximately 36 hours before admission to the

hospital. Figure 4 illustrates the course of a patient who had a chronically reoccuring pyelitis in association with hydronephrosis. Sulfadiazine given by her physician did not prevent the attack postpartum. The response to oxytetracycline was dramatically favorable.

INFECTIONS OF THE MAMMARY GLAND IN OBSTETRIC PRACTICE

The mammary gland is not a genital organ but puerperal mastitis must be considered as an aspect of obstetric infection. The incidence of mastitis in association with lactation at the Chicago Lying-In Hospital has averaged about 0.5 per cent.

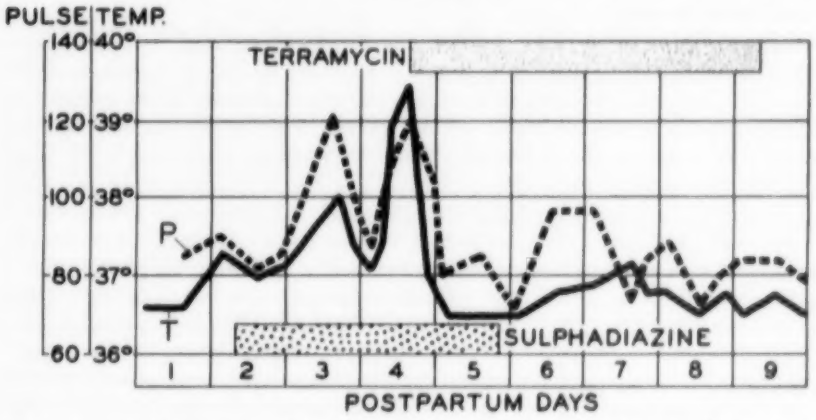

FIG. 4. Patient with recurrent pyelitis and hydronephrosis. Developed pyelitis after delivery despite use of sulfadiazine prophylactically. She responded dramatically to treatment with oxytetracycline.

Those that proceeded to suppuration yielded a *Staphylococcus aureus* in practically all instances. That so few women have this complication is remarkable for two reasons: first, because approximately two thirds of all puerperal women have hemolytic *Staphylococcus aureus* in their respiratory passages; secondly, because about two thirds of the newborn have hemolytic *Staphylococcus aureus* in their buccal or nasopharyngeal passages within the first 10 days of extrauterine life.[4] Consequently, even if the normal flora of the nipple did not contain the pathogen, the baby's contaminated mouth is a menace. Thus the obvious factor, injury to the nipple and breast, must be avoided. At one time it was felt that the nipple could be toughened by massage and exercise before birth, but concrete evidence to substantiate this point is lacking. Furthermore, the normal bacterial flora of the skin may constitute a natural protection against pathogens.

It is a well-established fact that epithelial tissue remains normal and heals much better under dry than wet conditions. For this reason exposure of a cracked or fissured nipple to the air favors its healing. When an abrasion or lesion occurs it is better to remove the baby from the breast. An electric breast pump (for both breasts) used properly at eight hour intervals (6 a.m., 2 p.m., and 10 p.m.) will maintain

lactation during this recovery phase. If the nipple does not heal promptly in two to three days, it is usually desirable to discontinue lactation in the interest of avoiding infection of the breast. Moreover, lactation will wane in most women if normal nursing is not established in a few days. Although breast feeding is preferred, good formulas are available for those infants who are denied the benefit of normal feeding.

Babies that nurse too long or injure the nipple contribute to mastitis. Unfortunately, a few women have bifid or inverted nipples. If the nipple can be drawn out by the baby, there is fair prospect that nursing may be conducted satisfactorily and safely. The judicious use of an electric breast pump may bring out the nipple to the point that the infant can feed normally. Failure to draw out the nipple precludes normal breast feeding.

Ordinarily the administration immediately of 200,000 units of crystalline penicillin and 600,000 units of procaine penicillin followed by the same amount of the latter twice daily will prevent suppuration provided treatment is started within 6 to 12 hours of the initial symptoms. If the breast condition remains untreated for 24 hours the incidence of suppuration increases very rapidly in relation to the lapse of time.[6] The administration of erythromycin in a dosage of 2 Gm. orally or 1 Gm. intravenously per day may hold promise but it needs full evaluation. Sulfonamides are not nearly so efficient as antibiotics. Oxytetracycline in a dosage of 4 Gm. per day may be used either in conjunction with penicillin or alone if the patient cannot tolerate penicillin. Broad-spectrum antibiotics may tend to replace penicillin because of the increased number of patients sensitized to penicillin. Because of indiscriminate or inappropriate use of penicillin, many organisms, especially staphylococci, harbored by patients have acquired resistance to it. Oxytetracycline appears to induce fewer patient sensitizations and less bacterial resistance than penicillin and streptomycin.

The fact that the patient may become afebrile after antibiotic therapy does not mean that an abscess has been entirely prevented. It sometimes means that the process has been sharply localized. Patients free of fever have been observed to carry a localized abscess for as long as two months. All of the evidence of infection must disappear. Any residual process that does not disappear needs investigation. Psychologically, these people are not good candidates for lactation in subsequent pregnancies, especially if they have developed an abscess. Breast abscesses occur in most instances after the patient has returned home. It is disturbing to the mother and family to meet the new complications and still supply proper care for the baby. Under these circumstances the better-run maternity services will not readmit this baby to the nursery. Hence if there are no family members to care for the baby, it may be necessary to admit it to a pediatric service.

CONCLUSION

Oxytetracycline has a very definite place in the practice of obstetrics for both obstetric infections themselves and for some infections incidental or related to pregnancy. Oxytetracycline will, of course, not replace good technique. It will not take the place of other modalities of treatment, but it has been a valuable aid and

has definitely contributed to the health and welfare of mothers. It would seem under certain conditions oxytetracycline may be substituted with advantage for the combination of streptomycin and penicillin. Probably because penicillin has often been used irregularly and inadequately, many bacterial strains may be resistant to penicillin. Erythromycin may be a better drug in such instances than penicillin. Oxytetracycline has a broad coverage and has rarely produced sensitization in patients, and bacteria seem less likely to develop resistance to it. Therefore oxytetracycline is a valuable antibiotic in the treatment of a variety of obstetric infections.

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Oxytetracycline in the Treatment of Pelvic Infections

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The advent of antibiotics and chemotherapy has completely changed the clinical picture as well as the ultimate outlook in cases of pelvic infection. The new trend of treatment began with the sulfonamides, broadened its scope with penicillin, and nowadays includes an ever increasing number of antibiotics of broad-spectrum range. These broad-spectrum drugs are most powerful and can be given by mouth, by intramuscular injection, or by intravenous infusion to permit the most effectual and flexible administration in the therapy of pelvic infection.

Pelvic infections in the female have always been more prevalent in city hospitals than in private hospitals, and long experience at Harlem Hospital has enabled us to observe the changing picture and permitted the evaluation of newer forms of therapy in large numbers of patients with the most serious forms of pelvic inflammation. Twenty years ago the basic concept in the treatment of these infections was to permit the body to mobilize its own defenses and to localize the inflammation with the aid of proper hydration and supportive therapy. Fortunately, in most instances, gonococcal and postabortal infections were self-limiting in nature. However, in a considerable proportion, chronic invalidism, the so-called pelvic cripple has necessitated radical surgery in the form of hysterectomy and bilateral salpingo-oöphorectomy as the final curative measure in many unfortunate young women.[1] Today, with better antibiotic drugs available, and with the means of making a specific choice of the most effective one by sensitivity tests, surgery for pelvic infection is becoming increasingly infrequent. Each of the newer antibiotics has its proper advantageous application for the proper patient. Our own experience has been greatest with oxytetracycline (Terramycin*).

DECREASE OF MORBIDITY AND MORTALITY BY ANTIBIOTICS

The effect of antibiotics can be graphically shown by the relative decrease in the number of patients admitted to the hospital wards from the clinic (table I). The reason for the decrease in ward admissions is that with the use of oxytetracycline and other antibiotics pelvic infections, which constitute more than half the admissions of the ward patients, are readily and effectively treated in the outpatient clinic.

Although the clinic population has steadily increased, the percentage of admissions has steadily decreased because of more effective modes of ambulatory therapy, which in turn limit the serious complications of infection requiring hospitalization.

* The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

Similarly, in the treatment of abortions an increasing extension of early curettage has been permitted by the free use of antibiotics with a sharp diminution in the number of deaths caused by abortions (table II).

TABLE I

Declining Necessity for Hospitalization of Patients with Pelvic Infections

Year	Patients Treated in Clinic	Patients Admitted from Clinic to Ward	%
1947	9,862	257	2.6
1948	10,682	547	5.12
1949	12,879	551	4.28
1950	16,597	215	1.29
1951	17,264	420	2.43
1952	19,049	235	1.23

It can be seen that prior to 1950 when sulfonamides and penicillin were chiefly used the death rate was higher than after 1950 when penicillin and broad-spectrum antibiotics substantially reduced the mortality rate. Furthermore, and perhaps it is of equal importance, we find that these patients are being given antibiotic therapy by the abortionist. The incidence of serious postabortal complications present on admission has steadily decreased.[2]

A similar trend is evident in the declining operative death rate (table III). It must be emphasized that at Harlem Hospital more than 50 per cent of the gynecologic operations performed are in part or in whole for pelvic inflammation.

Of the 3 deaths, 2 were the result of hemorrhage in patients with ectopic pregnancy admitted in the terminal phase, and one to uremia secondary to cancer. Thus in this year there was no operative death caused by infection.

TABLE II

Experience with Early Curettage in Patients with Septic Abortions

Year	Total No. Abortions Admitted	Total No. Curettages	Total No. Deaths	Total Mortality Rate, %
1947	691	462	9	1.3
1948	762	618	4	0.53
1949	789	709	5	0.64
1950	860	742	2	0.23
1951	1039	921	1	0.10
1952	1187	1069	1	0.084

The most commonly seen serious pelvic inflammations are caused by abortion and pelvic inflammatory disease. Therefore, the therapy of these lesions in terms of our own experience, as well as in the literature, will be reviewed first.

At Harlem Hospital, the treatment of simple incomplete abortion consists of antibiotics, oxytocics, prompt curettage, and blood, as indicated. The rationale is based upon the fact that the majority of abortions seen at this institution have been criminally induced, enhancing the likelihood of severe infections. Prior to the present year the antibiotic generally employed was procaine penicillin 600,000 units twice daily. Other antibiotics were employed as needed. Recently, in an attempt to evaluate the effectiveness of intramuscular oxytetracycline, 100 cases were treated solely with this antibiotic. The series was compared with a similar group of 100

TABLE III

Decline in Deaths after Operation

Year	Operations	No. Deaths	% Mortality
1947	934	11	1.15
1948	1084	16	1.48
1949	1215	13	1.06
1950	1202	10	0.83
1951	1412	5	0.35
1952	1522	3	0.20

patients treated with penicillin (table IV).[3] Twenty of the penicillin group were febrile on admission as compared with 33 of the oxytetracycline. The dosage of oxytetracycline was generally 100 mg. twice daily; occasionally 400 mg. was used daily. All patients in both series were curetted. The response of patients to therapy is shown in table IV.

Sixteen of the 100 patients complained of pain at the site of injection, but the pain was never severe enough to require a discontinuance of therapy. When the intramuscular injection was deep and without leakage into the subcutaneous tissue, complaints of pain seemed to be obviated. There were no drug reactions or extension of infection in any patient of this series.

The use of antibiotics prophylactically in this fashion has greatly minimized serious postabortal infections. Women with spontaneous abortions rarely have serious infections in any event. Those with induced abortions if promptly and adequately treated should not develop extrauterine extension either.

TABLE IV

Comparison of the Effectiveness of Penicillin and Oxytetracycline in the Treatment of Abortions

	Penicillin Group	Oxytetracycline Group
Febrile (after dilatation and curettage)	16	11
Av. stay in hospital	4.7 days	3.7 days

Unfortunately, because of ignorance or fear, serious infections are still seen although in diminishing number. Such infections extend to the parametrium, the adnexae, the peritoneum, and the pelvic veins.

Parametritis, which in the past rarely proved to be fatal, was a source of prolonged hospitalization and pelvic "crippling." It is now extremely uncommon. The following case is worthy of mention.

F. S., a 36 year old woman, para II, was admitted with an induced abortion after three months of amenorrhea. Her temperature was 103 F. and she was acutely ill. The abdomen was tender but no masses were felt. On pelvic examination, the cervix was surrounded by induration that froze the uterus so that it could not be outlined. She was placed on intramuscular oxytetracycline, receiving a total dosage of 4200 mg., and was discharged with minimal induration in six weeks. She became pregnant two months following discharge from the hospital and is now in the thirtieth week of gestation.

Although it is well known that postabortal parametritis does not predispose to sterility as do gonorrheal infections; nevertheless the occurrence of pregnancy so soon after such severe and extensive infection is striking.

In a recent contribution,[4] 2 cases were reported of the use of cortisone and antibiotics in resistant pelvic infections following abortion. The theory is advanced by some that cortisone has the ability to dissolve recently laid down granulation tissue and thus permit plasma concentration of antibiotics to act more thoroughly on the bacteria. The author states that the use of cortisone alone would be dangerous and quite possibly fatal. In view of the danger of cortisone in extending infections, however, this work cannot be accepted until confirmed on a much larger scale.

The major causes of death in postabortal infections are peritonitis[5] and pelvic thrombophlebitis.[6] Thus other workers who report that antibiotics administered early lower mortality and morbidity rates nevertheless had 6 deaths, 5 of which were due to peritonitis and 1 to pelvic thrombophlebitis.[7] There is apparently a geographic variation in the frequency of these two lesions, suppurative thrombophlebitis being seen more frequently in New Orleans, whereas our experience is that peritonitis is the most frequent cause of death in criminal abortion. In the treatment of postabortal peritonitis prior to chemotherapy, all patients with recognized peritonitis died. With the advent of the sulfonamides and penicillin, a more active surgical approach was possible. These antibiotics alone did not cure peritonitis but, employed in conjunction with hysterectomy and drainage, 66 per cent of such patients were saved.[8] At the present time, all patients admitted with spreading peritonitis are first given intensive therapy with penicillin and a broad-spectrum antibiotic, such as oxytetracycline or tetracycline intravenously. In the majority of patients the infection is controlled and the peritonitis subsides leaving residual tuboovarian inflammation, which may or may not require surgery at a later date.

Our experience with suppurative pelvic thrombophlebitis is limited. In patients with infected abortion, blood cultures are routinely performed and in the rare case in which positive organisms are obtained, sensitivity tests and appropriate antibiotic therapy are instituted with completely satisfactory results. Therefore, re-

course to vein ligation has not been necessary. A contrary point of view has been expressed by Collins and his co-workers.[9]

Endocarditis is an extremely rare complication of abortion and if recognized early and treated adequately with appropriate antibiotics can be cured. Oxytetracycline or other broad-spectrum antibiotics have been recommended in the puerperium of women who have had healed subacute bacterial endocarditis to prevent recurrence.[10]

Cases of postpartum endometritis respond as readily to oxytetracycline as do those of postabortal origin.[11, 12]

PELVIC INFLAMMATORY DISEASE

The term "pelvic inflammatory disease" is often loosely used to cover all types of genital inflammation above the cervix and perhaps in view of the diminishing numbers of such cases fine distinctions may no longer be necessary. However, on those gynecologic services in which large numbers of these cases are still seen, the distinction between postabortal infections, gonorrheal infections, and tuberculous disease is still important.

Gonorrheal infections of the tubes and ovaries are not so serious or extensive or prevalent as they have been. If gonorrhea is suspected, its diagnosis should be confirmed by bacteriologic means if possible. The culture examination for gonococci is much more sensitive and reliable than the examination of smears, although cultures are still not so sensitive as we would like them to be. Therefore, the clinical evaluation of the patient as well as the bacteriologic findings must be considered in therapy.

Gonorrheal disease in the female begins generally in the cervix and urethra before it extends to the tubes and ovaries. Such extension usually takes place after a menstrual period. Gonorrheal disease below the level of the internal os affords the best opportunity for cure if it can be recognized. There is ample evidence to indicate the effectiveness of oxytetracycline for the cure of gonorrhea at this stage. Thus, of 26 patients treated with a single dose of 1 Gm., smears and cultures were negative within 24 hours in all but 3. Similarly, 45 of 55 patients were clinically and bacteriologically cured in another series of women.[13–16] We prefer to give oxytetracycline, 1 Gm. daily for three to four days or for 48 hours after all symptoms have subsided.

Acute primary salpingitis usually develops two to three weeks after the initial exposure and shortly after the cessation of menstruation. The treatment of primary acute salpingitis is always conservative with antibiotics, since recovery is the rule.

H. A., a 27 year old single, colored woman, was admitted on the fourth day of her menstrual period with severe lower abdominal pain, vomiting, and fever. She had noticed burning on urination and discharge of two weeks' duration. The temperature was 102 F., the pulse was 90, and she looked acutely ill. There was tenderness with rebound and spasm in the lower abdomen. On vaginal examination, motion of a normal cervix and uterus caused exquisite tenderness but no adnexal masses were felt. Smears were positive for gonococci. Oxytetracycline, 1 Gm. daily, was administered and within 24 hours her temperature was normal and within 48 hours the vaginal and abdominal tenderness had subsided. She has remained well.

Recurrent salpingitis occurs as a result of reinfection of the tubes from the pa-

tient's cervix or actual new infections from the same or another source. Recurrent salpingitis is rarely seen in private practice but rather in patients unable or unwilling to take care of themselves. As a result of repeated infections, a pyosalpinx or more rarely a tubo-ovarian abscess forms. Cultures and smears are not so conclusive as in acute primary salpingitis. There is some question that the administration of appropriate antibiotics reduces the fever and makes the patient more comfortable. Furthermore, by sterilizing the lesions it makes subsequent surgery easier and avoids serious postoperative complications, such as peritonitis, ileus, and wound infections, even if there is little effect upon the size of the adnexal masses. When large adnexal masses form, oxytetracycline and other antibiotics as currently used do not significantly hasten the resolution of such masses.[17, 18] It must be emphasized that any single attack of salpingitis can be safely managed conservatively by antibiotics; surgery is resorted to only for repeated incapacitating disease.

M. S., a 35 year old woman, para O, had many attacks of lower abdominal pain with fever for the past five years. For one week she had severe lower abdominal pain, fever, and pain on urination and defecation. Her temperature was 102 F. and her pulse was 100. She looked acutely ill. Her abdomen was distended and tender, with bilateral masses extending midway to the umbilicus. On vaginal examination, bilateral, tender tubo-ovarian masses about 10 cm. in size were found. There was considerable tenderness and induration in the fornices and the rectovaginal septum as well. A diagnosis of bilateral tubo-ovarian abscess with pelvic peritonitis was made. She was placed on supportive therapy plus penicillin 100,000 units intramuscularly every three hours and 2 Gm. of oxytetracycline daily. Her temperature fell to normal and the sedimentation rate returned toward normal. She was operated upon three weeks after admission. At operation, large tubo-ovarian abscesses were found with many dense peritoneal adhesions. A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. Oxytetracycline and penicillin were continued postoperatively. She made an uneventful recovery and was discharged on the tenth postoperative day.

In a small number of women, as a result of "burnt-out" infection, there are disabling pain, sterility, menstrual disorders, and occasionally a hydrosalpinx. Such cases are not generally amenable to antibiotic therapy, although, according to Perrini,[12] oxytetracycline has a decongesting effect in the pelvis and may reduce abnormal bleeding. The treatment of such disease is by physical therapy and as a last resort hysterectomy with removal of the adnexae.

Oxytetracycline has been widely used in various other infections of the genital tract, which are either not so serious or seen so frequently as postabortal infections and pelvic inflammatory disease. An anatomical approach to these pelvic infections including a review of the appropriate literature may now be considered.

VULVA

Bartholinitis. Five hundred mg. of oxytetracycline orally four times daily in acute early bartholinitis has given excellent results. Swelling and pain subsided within 24 to 48 hours and hospitalization was not required. According to the authors, all

patients who were treated early did not require surgery and were back at work within four days after therapy.[19]

Chancre. Oxytetracycline given orally[20] or intravenously[21] results in the disappearance of spirochetes from the surface lesions when given in primary or secondary lues. However, its value as definitive therapy is not well established at the present time.

Chancroid. Five hundred mg. of oxytetracycline four times daily by mouth will result in the subsidence of the vulval lesions and the lymphadenitis, usually within eight days. Generally in 24 to 48 hours the pain and edema decrease and the patient is more comfortable. Some cases are more resistant and longer therapy is necessary.[22–28]

Lymphogranuloma Venerum. This is a disease characterized by a vulval lesion associated with inguinal adenitis and/or proctitis in the acute case. In the chronic cases, rectal stricture is common in women. The Frei test is positive in both acute and chronic cases. The disease responds well to 250 mg. of oxytetracycline four times a day by mouth although originally 500 mg., four times daily were employed.[21, 22, 26–29] Vulval ulcers, buboes, and proctitis showed immediate and rapid improvement. "The average time for resolution of the acute pathology was 29½ days."[30] The earlier the lesion is treated the more quickly the objective signs of the disease will disappear. For chronic cases with stricture, oxytetracycline should be used in conjunction with surgery[31] as no antibiotic can cure a fibrous stricture. Oxytetracycline is the antibiotic of choice in this disease.

Granuloma Inguinale. This is a specific granulomatous disease caused by a gram-negative bacillus, *Donovania granulomatis.* Two Gm. of oxytetracycline daily for 12 days is given and within a week the Donovan bodies disappear with epithelialization and healing of the lesions.[22, 28, 32–34] Oxytetracycline is the drug of choice, since patients "so treated show fewer side-reactions, and a lower incidence of need for re-treatment."[35] Average total dose of oxytetracycline was 32 Gm.

VAGINA

Trichomonas. Oxytetracycline vaginal suppositories and powder dusted over the vagina has been reported by some authors to have cured *Trichomonas vaginalis* vaginitis in many cases.[36, 37, 39] However, cure has not been consistent and reinfections have occurred. Recently the use of oxytetracycline-polymyxin suppositories for the cure of recurrent trichomonal infection has been suggested. For example, of 37 patients treated with oxytetracycline suppositories, 22 had excellent results and 12 had good results.[40] At the present time no wholly satisfactory antibiotic therapy for this form of vaginitis has been found.

Monilial Vaginitis. This is not uncommon and occasionally may complicate trichomonal vaginal infestation. The cure of monilial vaginitis with the use of vaginal oxytetracycline tablets has been reported in 5 of 10 patients.[38] Further substantiation would seem to be required. In many cases vaginal mycosis has followed antibiotic therapy apparently owing to the suppression of the normal vaginal flora. The use of antimycotic agents, such as gentian violet and proprionic acid gels, prophylac-

tically in patients receiving antibiotics may be of value in minimizing vaginal mycosis[11]

CERVIX

Acute and chronic cervicitis are frequently seen in office and clinic practice. Many of the acute cases are of gonorrheal origin as demonstrated by cultures of the cervix. Although penicillin is generally employed in the cure of gonorrheal cervicitis, in penicillin-resistant organisms, oxytetracycline by mouth or intramuscularly is effective. One Gm. daily is given orally for three to four days. Thus of 26 patients, 23 were cured with a single dose of 1 Gm., whereas 3 patients required retreatment with an additional 1.5 Gm.[13] All patients were bacteriologically and clinically cured.

The cervix as the cause of sterility is receiving increased attention. Investigation of the sterile couple in some instances demonstrates only poor or absent sperm migration in the postcoital test at the time of ovulation. Bacteriologic examination of the cervical mucus in such patients reveals spermicidal organisms in 84 per cent. Antibiotic therapy has been used locally and intracervically. Oxytetracycline or chlortetracycline* was given orally in 2 Gm. doses daily for four days immediately after the menstrual period. Of 95 patients treated, 21 subsequently became pregnant, which was significantly higher than that of a control group.[12] In a similar experiment, it was found that oxytetracycline given in 6 Gm. dosage for three days prior to ovulation improved the chance of conception if the only recognized abnormality is poor or absent sperm migration.[13]

POSTOPERATIVE WOUND INFECTIONS AND EXUDATES

Occasionally an unexpected wound infection[14] or pelvic exudate is found following a clean operation in which the prophylactic administration of antibiotics has not been necessary. The choice of antibiotic should depend upon the isolation and sensitivity test of the organism, but when this is not feasible, oxytetracycline used empirically often gives dramatic results.

L. De C. was readmitted 18 days after a total abdominal hysterectomy and bilateral salpingo-oophorectomy with pain in the left lower quadrant radiating down the leg. Temperature was 101 F. There was an indefinite mass above Poupart's ligament. On vaginal examination the vagina was normal and well healed and there was a tender indurated mass filling the left pelvis. She was given penicillin for one week, without significant improvement. On the eighth day, oxytetracycline, 1 Gm. daily, was added. On combined therapy, her temperature gradually subsided and the exudate diminished in size so that she could be discharged on the sixteenth hospital day with minimal induration present.

Oxytetracycline vaginal suppositories have been satisfactorily used by us for preoperative vaginal antisepsis prior to total abdominal hysterectomy and vaginal operations.

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* The trade name of Lederle Laboratories Division, American Cyanamid Co., for chlortetracycline is Aureomycin.

Oxytetracycline has no direct effect in the treatment of urinary retention following vaginal plastic procedures. However, used prophylactically it reduces the pyuria associated with urinary retention.[45] Oxytetracycline is effective in the therapy of urinary infections encountered in gynecology.[46, 47]

SUMMARY

1. The morbidity and mortality owing to pelvic inflammatory disease in the female have been substantially reduced by the use of antibiotics. Oxytetracycline appears more effective than penicillin in rapid reduction of fever.

2. Oxytetracycline has been found effective by mouth in local and regional gonococcal infections, including acute salpingitis and tubo-ovarian abscess; in the latter case treatment was both pre- and postoperative.

3. Oxytetracycline has proved effective in the treatment of many gynecologic conditions, including bartholinitis, chancre, chancroid, granuloma inguinale, acute and chronic cervicitis, and wound infections.

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Oxytetracycline in the Treatment of Infections of the Genitourinary Tract

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In the four years since its introduction for clinical trial, oxytetracycline (Terramycin*) has become accepted as an effective antibacterial agent in the treatment of infections of the urinary tract. Other contributors to this symposium have elaborated upon the immense amount of laboratory and clinical investigation already accomplished to establish the physical and biologic characteristics of this antibiotic. No useful purpose would be served by reiteration of these details already well documented in the recent literature. The purposes of this discussion would best be served by the development of a practical philosophy of treatment for urinary tract infections designed to fit the needs of both general practitioner and specialist. Thus oxytetracycline will be treated as a representative of an ever-increasing family of antibacterial agents. It may possess certain advantages in regard to low toxicity and wide range of bacterial effectiveness, but in general it is similar in most respects to other broad-spectrum antibiotics.

A METHOD OF APPROACH

The physician of today is rightly impressed by the rapid response of urinary tract infections to modern remedies. He is also cognizant of the disturbing proportion of such infections that nevertheless still fail to improve under therapy or recur after remission. These failures comprise the real therapeutic challenge. A definite number can certainly be avoided by a more logical approach to the patient's problem.

The busy practitioner may face the necessity of accurate diagnosis of a urinary tract infection suspected on the basis of signs and symptoms presented by a new patient. He ordinarily confirms his impression by examination of the sediment of a centrifuged catheterized urine specimen in the female or a second glass voided specimen in the male. A simple methylene blue stain of the dried sediment serves to identify the organism as bacillary, coccal, or mixed and allows the physician to make a quick choice of therapeutic agent. In the absence of overwhelming sepsis or other modifying circumstances, the physician need not at this time employ a broad-spectrum antibiotic, such as oxytetracycline. This statement is based on practical considerations. Oxytetracycline and similar antibiotics, by reason of the considerable expense incurred by drug companies in their development, are costly. In the majority of instances uncomplicated urinary tract infections are easily resolved by one of the less expensive chemotherapeutic agents, such as a sulfonamide, Gantrisin being a good popular example. Doses of 1.0 Gm. every six hours over a period

* The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

of five to seven days usually accomplish a good therapeutic result. Some considerations other than economic are involved of course. The preliminary use of a sulfonamide also may serve the highly important purpose of giving time to detect infections that will resist drug therapy because of anatomical obstructive factors in the genitourinary tract. Such a situation often prevents successful resolution of urinary tract infection no matter what agent is used. To employ oxytetracycline first under such circumstances might possibly result not only in failure to control the infection but cause the development of bacterial resistance to oxytetracycline and to other antibiotics as well. This may compromise the chance of later successful treatment with oxytetracycline subsequent to removal of the obstructive lesion.

It is logical therefore for the physician at this point to investigate carefully the reason for any initial therapeutic failure with drugs. He may accomplish this by detailed investigation of the urinary tract, including endoscopic inspection of the urethra, cystoscopic evaluation of the bladder, and roentgenographic survey of the upper urinary tract by retrograde pyelography and microscopic study of the urine specimen obtained at this time from each kidney. Such an investigation is done to detect the presence of any abnormality of the genitourinary tract or of infection not susceptible to drug therapy.

REASONS FOR THERAPEUTIC FAILURE

Briefly, it is known that stasis of urine, calculous disease, neoplasm, and tuberculosis constitute a quartet of factors whose presence militate against satisfactory antibacterial treatment. The elderly gentleman with prostatism or the little boy with congenital urethral valves share one common factor, infected residual urine, destined to persist until the obstruction is surgically corrected. Secondary infection in a bladder involved by a necrotic neoplasm will persist unless the primary lesion can be eliminated. Likewise, urinary tract infections that develop in conjunction with calculi rarely disappear until the calculi are removed. Although urinary tract tuberculosis is said to be characterized by an amicrobic pyuria, it is worthy of note that 30 to 35 per cent of tuberculous infections of the urinary tract are associated with secondary pyogenic invaders. Failure to suspect the underlying process may perpetuate the activity of both infections.

Added to this group are such entities as enterovesical fistulae productive of infection notable for chronicity and severity of bladder irritation. A history of pneumaturia should arouse suspicion of such communication. Lesions in and around the urethra are also a common source of refractory infections. In the female, urethral contamination may result from improper diaper hygiene in infancy, from the trauma of childbirth or of initial intercourse, or from senescent changes in the mucous membranes of the urethra with a lowered resistance to the flora of the genital tract. Diverticula of the female urethra secondary to periurethral inflammatory disease may furnish a continuing source of infection. They are found only when the suspicion of such a lesion leads to very careful endoscopic inspection of the urethra. In the male the accessory sex glands, especially the prostate, are notorious contributors to the chronicity of infection in middle age.

One additional factor is worthy of discussion, primarily because it, in itself, is responsible for therapeutic failure in the majority of instances in which the urinary tract is otherwise normal, namely, resistance of the bacteria present to the drug used either *ab initio* or after inadequate or unsuccessful treatment. Because of this the next important step in the management of urinary infection after initial failure and after proper investigation and elimination of contributing causes, if present, is identification of the infecting organism by culture.

OXYTETRACYCLINE AND THE GENITOURINARY BACTERIAL SPECTRUM

The chief offenders in infections of the urinary tract are the gram-negative bacilli: *Escherichia coli*, *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Alcaligenes faecalis*, and paracolon bacilli. The gram-positive cocci are less frequently found but include various strains of staphylococci, *Streptococcus faecalis*, and other streptococci. Numerous other species may be implicated in isolated instances.

The physician is by nature a methodical individual, and he enjoys the opportunity to fit causative organism and drug of choice in regular categories. Therapeutics would be simple if bacteria could be made to conform to desire; unfortunately, this is not the case. The practitioner is cognizant of the fact that no definite relationship exists and that at best he must deal in generalities based largely on experience. To this end it may be said that oxytetracycline is *usually* effective against infections caused by *E. coli*, *A. aerogenes*, *A. alkaligenes*, the paracolon bacilli, *Staphylococcus aureus*, and hemolytic and nonhemolytic streptococci. It is moderately effective against *Ps. aeruginosa* (*Bacillus pyocyaneus*) and *Str. faecalis* and generally not effective in infections due to *Bacillus proteus*. There are exceptions to all of these instances. Because of these exceptions, the variations from one strain to another, and the problem of resistance and cross resistance, cultural identification alone may not suffice in the choice of an antibiotic. Greater accuracy in selection may result from sensitivity studies—preferably by the tube-dilution method. Admittedly this is a time-consuming and expensive procedure, but it is worth the effort because the decision may be a vital one. Also, the information gained by in vitro techniques does not always find clinical correlation in vivo. Nevertheless, it is a guidepost of worth if used with full knowledge of the shortcomings inherent in its performance.

METHODS OF OXYTETRACYCLINE ADMINISTRATION

Oxytetracycline is an agent effective against a broad bacterial spectrum. Once a decision is made to employ it in therapy, the next question naturally is the mode of administration. An initial oral loading dose of 1.0 Gm. is usually sufficient to secure an adequate blood concentration. Herrell et al[1] have shown that doses greater than this do not produce a significant increase in initial levels. For most genitourinary infections the blood concentration can be maintained at a relatively high level by the administration of 250 mg. every six hours. Under these circumstances the concentration in the tissue and urine remains high.

It would seem logical at this point to attempt to correlate bacterial sensitivity, drug dosage, serum concentration, and antibacterial effectiveness. Thus, if an organism is only moderately sensitive to oxytetracycline, it might seem wise to increase the dose and thus the serum and urinary levels of the antibiotic. To a certain extent this is true. Linsell and Fletcher,[2] for instance, showed that infections caused by *B. pyocyaneus* respond best to a dosage of 1.0 Gm. at six hour intervals. This leads to urine concentrations as high as 300 to 400 μg./ml., far greater than that needed for most sensitive organisms. However, there is a limit to this benefit, for an increase in dosage of oxytetracycline does not always result in a corresponding increase in either the blood or urine concentrations. Between the low and high dosages, there is a point of optimum absorption beyond which the excess is excreted in the feces.

Urologic patients unable to accept oral medication may be given intravenous crystalline oxytetracycline hydrochloride. A dosage of 0.5 to 1.0 Gm. every 12 hours is usually sufficient for the adult. Intravenous use should be discontinued whenever oral administration becomes possible.

The duration of administration is variable. In most instances 2.0 Gm. per day for five to seven days is sufficient to resolve urinary tract infections caused by susceptible organisms. Recent work, however, has emphasized the need for fully effective dosage over a sufficiently long period of time in order to avoid recurrence caused by resistant bacterial strains. Bryson and Demerec[3] have shown that the development of bacterial resistance to an antibiotic depends on the selection of spontaneously occurring mutants. In the case of oxytetracycline, this usually requires multiple genetic steps for the development of complete resistance. Thus, first step mutants provide material for the selection of more resistant second step mutants, etc. Herrell et al[1] and Pansy et al[4] have demonstrated that cross resistance also occurs. Thus, if an organism is made resistant to oxytetracycline through a series of mutations, it will usually show a similar resistance to chlortetracycline* and chloramphenicol† and vice versa. Interestingly enough this cross resistance between the broad-spectrum antibiotics does not extend to streptomycin. In fact, an induced resistance to one of the broad-spectrum antibiotics frequently results in an increased sensitivity to streptomycin, suggesting that a combination of oxytetracycline and streptomycin might be highly effective in certain infections. This has been used to advantage by Carroll in *Pseudomonas* infections.

Rhoads et al[5] have suggested that an answer to the problem of development of resistant strains may be found not only through adequate dosage programs but also by the use of oxytetracycline in combination with a chemotherapeutic agent, such as one of the sulfonamides. It is recommended that one agent overlap the other in the course of therapy. There is evidence that such combination therapy is productive of results superior to that attained with either drug used singly.

* The trade name of Lederle Laboratories Division, American Cyanamid Co., for chlortetracycline is Aureomycin.

† The trade name of Parke, Davis & Co. for chloramphenicol is Chloromycetin.

In general, then, the aim of therapy is to give oxytetracycline in sufficient dosage over a reasonable length of time. In most instances in which the infection under treatment has proved resistant to other forms of therapy and oxytetracycline appears to be the drug of choice, it is undoubtedly advisable to overlap its use with a sulfonamide or in the case of *Pseudomonas* infections with streptomycin in order to decrease the incidence of initial therapeutic failure or recurrence with resistant strains.

The application of oxytetracycline to infections of the several genitourinary organ structures has been made. With few exceptions the invasion of tissue by a pathogenic organism, whether it be in the urethra, prostate gland, bladder, or kidney, creates initially the same essential problem—namely, the need for immediate concentration of an effective amount of the antibiotic at the site of active inflammation. Thus an acute pyelonephritis demands the same dosage and for the same duration as an acute prostatitis or cystitis. Only the method of assay of results will vary. Certain aspects of this subject are worthy of further elaboration. It is assumed by some that the goal in treatment of a urinary tract infection is the development of an adequate concentration of the drug in the urine. This is true to the extent that concentration in the urine reflects an adequate concentration in the blood system. The bacteria and pus cells found in the voided specimen only mirror the inflammatory process present in the tissues. The goal then is adequate *tissue* concentration of the antibiotic employed. The bacteriostatic effect produced locally enables the natural immune forces of the body to overcome the pathogen and heal the tissue damage. If this philosophy is accepted, the use of antibiotics as irrigating solutions within the cavities of the urinary tract, the use of suppositories containing the drug in similar situations, or the employment of an antibiotic in very low dosage over a long period of time as a preventive may be not only ineffectual, but the low concentrations obtained for relatively short period of time topically may actually foster development of mutant resistant forms. There is no evidence that the mucosal surfaces of the genitourinary tract absorb drugs in concentrations sufficient to be effective.

A PHILOSOPHY OF FAILURE

The preceding discussion provides background for the elaboration of a philosophy of therapeutic failure. Every bit as important as the philosophy of success already outlined, failure is a philosophy the practitioner may find difficult to accept. Despite a natural and healthy reluctance to admit defeat, the physician is forced at times to conclude that a certain number of infections (particularly the chronic ones) fail to respond to antibiotic therapy. An inkling of the frequency of this failure is provided by Rhoads et al[5] in his analyses of the treatment of chronic pyelonephritis with agents presently available to the physician. Less than 10 per cent of cases so involved resolved after "modern" therapy. This information may reflect on the medical profession adversely only if the physician is guilty of failure to avail himself of a logical program of treatment when a patient initially presents himself for consideration. For if chronicity already characterizes the condition of the inflammatory process on the first visit whether it has origin in the prostate gland, bladder, or kidney, the

difficulty of cure is substantially enhanced. The very nature of chronic inflammation, preventing as it does an adequate concentration of the drug at the site most needed, predisposes to therapeutic failure unless investigation demonstrates some logical way to rid the patient of the basis of his infection. If this is impossible because of the extent of the process or bilateral involvement, the physician may conclude that he has little in a positive way to offer the patient. However, sometimes under these circumstances, a variation in approach may offer surprising results. For instance, in a recent evaluation of patients with chronic recurrent cystitis who were resistant to antibiotic therapy, the bacteriocidal agent, mandelic acid, was found effective. Used in an acid environment over a period of 2 to 3 weeks, it has produced freedom from recurrence in a surprising number of cases.

CONCLUSION

Oxytetracycline is an antibiotic of proved worth in the treatment of infections of the genitourinary tract. It has the advantage of a wide range of antibacterial effectiveness without the disadvantage of toxicity or side reactions. If used in a logical fashion, oxytetracycline may be expected to cure the majority of acute infections caused by organisms sensitive to it, and, if utilized in conjunction with chemotherapeutic agents or other antibiotics, it may resolve some infections characterized by chronicity.

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Intramuscular Oxytetracycline in the Treatment of Acute Gonorrheal Urethritis in the Male

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Regardless of the existence of excellent drugs already available for many diseases, the pharmaceutical industry continues to search for newer therapeutic preparations and additional therapeutic forms of existing preparations. Thus, when one excellent drug may be for some reason unavailable or unsuitable for a patient, the physician will have a choice of newer drugs and additional forms. As long as this search proceeds, clinics and clinical laboratories will be obliged to evaluate the efficacy of these new preparations in the treatment of diseases. Oxytetracycline* (Terramycin) for intramuscular injection is such a preparation, which was developed for use in cases in which the oral form of the antibiotic cannot be used, such as comatose patients and patients with dysphagia, nausea, lack of co-operation, and poor absorption.

Oxytetracycline for intramuscular injection is a sterile, pyrogen-free, dry mixture, composed of the crystalline antibiotic, magnesium chloride, and procaine hydrochloride. It is available in 100 mg. vials, the contents of which readily dissolve in distilled water or saline. Two ml. of a diluent are added to the vial, making a solution containing 50 mg. of the antibiotic per ml. We employed sterile distilled water in our investigations.

Acute gonorrhea was our choice of disease for study because of the ease and simplicity of following the effects of treatment. The diagnostic criteria and those of cure are marked, clear-cut, and objective—the presence and the subsequent disappearance of a purulent discharge containing *Neisseria gonorrhoae*.

METHODS

All of the patients were from the Venereal Disease Clinic of Harlem Hospital and were seen, examined, and followed throughout this study by the authors. Each patient was questioned regarding his previous history and was excluded if he had received any therapy, either self-medication or otherwise, for the present urethritis. Only those patients were accepted for study who had a definite, profuse urethral discharge with leukocytes in which intracellular gram-negative diplococci were present. Cultures were then made on Bacto-G C medium (Difco) enriched with 20 per cent serum and hemolyzed horse erythrocytes.

In view of Seid's[1] report of favorable therapeutic effects in gonorrhea of one or two injections of 100 mg. of oxytetracycline intramuscularly, our treatment schedule

This investigation was supported in part by a grant from Chas. Pfizer & Co., Brooklyn, N. Y., and this company kindly furnished the oxytetracycline employed.

* The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

consisted of intramuscular injections of oxytetracycline in the following dosage schedules:

(1) A single injection of 100 mg. of intramuscular oxytetracycline into the upper outer quadrant of the buttock. The total dose was 100 mg.

(2) Two injections of 100 mg. each given simultaneously into each buttock. The total dose was 200 mg.

(3) Two injections of 100 mg. each given 24 hours apart. The total dose was 200 mg.

(4) Two simultaneous injections of 100 mg. on two successive days. The total dose was 400 mg.

Each patient was requested to return to the laboratory until three follow-up cultures were obtained, or until an interval of one week had elapsed between treatment and the last follow-up visit. Upon the first and each subsequent return visit, the patients were specifically questioned regarding any ill effects from the medication. The results of the treatment were evaluated on the basis of the clinical response and of the smear and culture of the urethral discharge. A patient was considered cured if the purulent discharge disappeared and posttreatment smears and cultures were negative and there was no relapse during the entire observation period.

We thus treated 40 patients who had acute gonorrhea. However, only 27 of these were adequately followed after treatment and these form the basis of this report.

RESULTS

The investigation reveals that results of therapy are in greatest measure a function of the dosage of oxytetracycline used. This is evident in table I, which presents the results following various dosage schedules.

TABLE I

Intramuscular Oxytetracycline in the Treatment of Acute Gonorrhea in the Male

Total Dose, mg.	Schedule	Number Cases	Cures	Failures	Side Reactions
100	Single injection	7	0	7	None
200	2 simultaneous injections of 100 mg.	5	0	5	None
200	2 injections of 100 mg., 24 hours apart	7	1	6	None
400	2 simultaneous injections of 100 mg. each, repeated after 24 hours	8	7	1	None

When a 400 mg. dosage of the antibiotic was employed, using two simultaneous injections of 100 mg. each repeated after 24 hours, we obtained seven cures and one failure. The one failure was free of any discharge for three days but relapsed on the fourth or fifth day following treatment. When he was seen on the fifth day, there was present a profuse discharge that was positive for gonococci. All patients who responded favorably were cured rapidly, the thick urethral discharge disappearing within 24 hours after the second set of two injections.

The 7 patients who received only 100 mg. of intramuscular oxytetracycline failed to respond to treatment. With double the dosage, we obtained five failures out of five trials when all the medication was given at one time, and one cure and six failures when the two injections were administered one day apart. Even though these cases proved to be treatment failures, most of them showed a diminution and some of them complete disappearance of the urethral discharge 24 to 48 hours following treatment. At 72 hours, however, all had relapsed and presented a profuse discharge with positive laboratory findings.

No drug toxicity of any sort was observed in any of our patients. With the exception of the moderate local pain resulting from the needle puncture, these patients made no complaint even when questioned specifically on this point. Locally there was no erythema, induration, or evidence of any skin lesions.

DISCUSSION

From these few and preliminary studies, it would appear that in adequate doses intramuscular oxytetracycline is effective in the treatment of acute gonorrhea. Our results indicate that 400 mg. is the minimal dose to be used in this disease. Further investigations are indicated. These may demonstrate that 0.5 Gm. of oxytetracycline would be the better total dose for intramuscular administration. Published reports[1, 2] have indicated that smaller amounts of this antibiotic are equally effective. The method chosen to evaluate treatment success or failure may explain this discrepancy. Had our period of observation been reduced, many of our failures would have been recorded as cures. In many of our patients, too, the smaller doses dramatically eliminated the discharge with corresponding negative cultures. This, however, was a transient state only, and relapses subsequently occurred with a picture of full-blown gonorrhea. This emphasizes the need for adequate follow-up periods in these studies. However, confusion may also be occasioned by re-infection during the posttreatment period, leading to a mistaken reduction in the cure rate.

It is noteworthy that none of the patients who received 200 mg. of the antibiotic at one time (in two loci) complained of undue pain. Many of them had had gonorrhea previously and had been treated with other antibiotics administered by injection. Upon direct questioning they implied that the oxytetracycline injection was not more painful than their previous treatment.

SUMMARY

Intramuscular oxytetracycline was used in the treatment of acute anterior gonorrheal urethritis in the male. Doses of 100 and 200 mg. were found to be inadequate, but 400 mg. of the antibiotic cured 7 out of 8 patients.

There were no toxic manifestations of the drug.

Intramuscular oxytetracycline may be used in the treatment of gonorrhea in the male when the oral form is not available.

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Oxytetracycline in Ophthalmology: A Review of the Literature

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CHEMICAL AND PHYSICAL PROPERTIES OF OXYTETRACYCLINE

Solubility and Vehicles. Oxytetracycline (Terramycin*) is an amphoteric substance forming crystalline acid and basic salts that are readily soluble in water. At its isoelectric point, however, oxytetracycline is rather insoluble in water. Oxytetracycline, its hydrochloride, and its sodium salt are reasonably soluble in acetone, methanol, ethanol, and other polar organic solvents.[35]

Douvas et al[13] state that 50 mg. of oxytetracycline hydrochloride powder dissolved in 10 cc. of Gifford's alkaline buffer solution No. 2 (*p*H 8.4) or in a special ophthalmic borate buffer solution (sodium chloride, 125 mg.; sodium borate, 50 mg.; distilled water, 10 ml.; *p*H 8.175) produce clear, stable solutions. This is not true for other solvents, such as distilled water; phosphate buffer solutions at *p*H 5.9, 6.64, 7.38, or 8.04; borate buffer solutions at *p*H 6.77, 7.36, or 8.08; Gifford's acid buffer solution No. 1 (*p*H 5); Gifford's acid buffer solution No. 2 (*p*H 6); Gifford's alkaline buffer solution No. 1 (*p*H 7.6); or special ophthalmic borate buffer solution combined with 1:3500 Zephiran (*p*H 8.26).

Stability. In the dry state oxytetracycline and its hydrochloride show no detectable loss of activity on prolonged storage at 25 C. Oxytetracycline hydrochloride shows less than 5 per cent inactivation after four months at 56 C., while oxytetracycline shows no loss in potency on heating for four days at 100 C.[35]

According to Gocke et al,[16] a solution of oxytetracycline hydrochloride, 4 mg./ml., showed no loss of activity over a period of 21 days in a deep freeze at −25 C., in a refrigerator at 5 C., or at room temperature (± 25 C.). At 37 C. the first appreciable loss in activity was noted between the seventeenth and twenty-first day.

Using a diffusion-plate assay method with Whatman No. 2 filter paper discs 3 mm. in diameter and hemolytic *Staphylococcus aureus* as the test organism, Douvas et al[13] found oxytetracycline hydrochloride solution, 2.5 mg./ml., to remain stable for five days at room temperature but lost 50 per cent of its effectiveness at the end of 15 days. The same solution in the refrigerator for 50 days lost none of its effectiveness.

Regna and Solomons[35] claim that aqueous solutions of oxytetracycline hydrochloride at *p*H 1 to 2.5 are stable for at least 30 days at 5 C. and 25 C. Solutions at *p*H 3 to 9 show no detectable loss in potency at 5 C. for at least one month. Gocke et al[16] found that the in vitro sensitivity of organisms to oxytetracycline is not affected by the *p*H of the medium at levels ranging from *p*H 5.6 to 8.2. Bliss, Warth, and Chandler[2] state that oxytetracycline is almost inert to changes in *p*H of the medium.

* The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

OCULAR TOLERANCE

P'an, Scaduto, and Cullen[27] found that 0.5 per cent solution of oxytetracycline hydrochloride in sodium borate buffer, *p*H 8.0, can be instilled in rabbits' eyes with practically no local reaction. The same in water, however, caused a mild degree of hyperemia that lasted from several to 24 hours. The latter may have been due to acidity per se, because dilute hydrochloric acid at approximately the same *p*H (2.5) caused comparable local reaction.

Douvas et al[13] used oxytetracycline hydrochloride, 25 mg./ml., in special borate buffer (*p*H 8.175) as drops every two hours or 0.1 per cent ointment four times daily in more than 200 cases and found it well tolerated without subjective irritation or sensitization. Thygeson[50] in almost 500 cases of external ocular infection reported no complications from the topical use of oxytetracycline other than a slight staining of the corneal epithelium after one-half or one hourly instillation of the drops. Town[52] in 132 cases of ocular infection encountered no conjunctival irritation and 1 case of sensitivity.

Cannon, Nichols, and Leopold[12] state that more than 200 human eyes tolerated instillations of oxytetracycline hydrochloride solutions up to 25 mg./ml. They also claim that subconjunctival injections are tolerated in quantities of 0.05 ml. in concentrations up to 50 mg./ml. (in rabbits up to 100 mg./ml.) Sorsby et al,[47] however, feel that oxytetracycline is too irritating for satisfactory subconjunctival injection.

Marr, Wood, and Storck[30] using young, adult white rats found no inhibition of corneal epithelial regeneration by oxytetracycline in concentration of 250 μg./ml. This was corroborated in rabbits by Cannon, Nichols, and Leopold[12] who used hourly drops of 5 mg. of oxytetracycline hydrochloride, 12.5 mg. of sodium chloride, and 5 mg. of sodium borate, per ml. of distilled water, during the day, and at night oxytetracycline hydrochloride ointment, 30 mg./Gm. of base was applied.

The latter investigators also reported that intracameral injections of 0.05 ml. of oxytetracycline hydrochloride solution produced no irreparable damage below 25 mg./ml. This concentration produced transient iritis and edema of the lower portion of the cornea due to corneal endothelial damage. Higher concentrations produced softening and distortion of the cornea and disorganization of the iris. Similarly intravitreal injections through the pars plana of 0.05 ml. of oxytetracycline hydrochloride solution produced no harm up to 25 mg./ml. or 1.25 mg. per injection, which caused permanent damage to the lower retina. Higher concentrations damaged the vitreous humor and retinochoroidal structures more extensively.

Azzolini and Faldi[3] claim that in man and rabbit oxytetracycline is well tolerated by conjunctival instillation (aqueous solution, 0.5 per cent), by subconjunctival injection (2.5 mg. in 0.5 ml. of water), and by injection into the anterior chamber (1 mg.). In the rabbit injection into the vitreous (1 mg.) is also well tolerated.

INTRAOCULAR PENETRATION OF OXYTETRACYCLINE

Douvas et al[13] showed that in rabbits a five minute corneal bath with oxytetracycline hydrochloride solution, 5 mg./ml., produced no immediate aqueous level and

none 30 minutes later. If the cornea is abraded, however, 28 μg./ml. were found in the aqueous humor 30 minutes later. Intravenous administration of oxytetracycline 30 mg./Kg. of rabbit produced, 100 minutes later, an aqueous level of 3 μg./ml.

Cannon, Nichols, and Leopold[12] found no penetration through the normal cornea into the aqueous humor at one-half, one, or two hours after drops of oxytetracycline hydrochloride solution, 5 and 25 mg./ml., every five minutes for six doses or after instillation of oxytetracycline hydrochloride ointment, 1 and 30 mg./Gm. Subconjunctival injection of 0.05 ml. of oxytetracycline hydrochloride solution, 50 mg./ml., produced an aqueous humor level of 9 μg./ml. at the end of two hours, otherwise there was no detectable aqueous or vitreous humor level at one-half, two, or six hours.

The latter authors also investigated the intraocular penetration from systemic administration of oxytetracycline. Orally oxytetracycline hydrochloride powder in capsules, 50 mg./Kg. of rabbit, produced no detectable amounts in the aqueous or vitreous humor one, two, four, or six hours later. Intravenous injection of oxytetracycline hydrochloride, 50 mg./Kg. of rabbit, produced the results shown in table I.[12]

TABLE I

Concentration of Oxytetracycline after Intravenous Administration of 50 mg./Kg. of Body Weight[12]

Tissue	Oxytetracycline Level in μg. per ml.		
	½ hr.	2 hr.	6 hr.
Blood serum	100+	100	20
Aqueous	9	0	0
Vitreous	0	0	0
Cornea	1	0	0
Conjunctiva	5	<2	<2
Sclera	3	0	0
Iris	3	0	0
Lens	0	0	0
Chorioretina	0	0	0
Tendon	0	0	0
Muscle	5	0	0
Optic nerve	0	0	0

Sorsby and his co-workers[46, 47] also state that systemically administered oxytetracycline in rabbits gives therapeutically inadequate intraocular levels. Leopold[25] feels that, because of its poor intraocular penetration, orally administered oxytetracycline is an unfavorable choice for pre- and postoperative prophylactic therapy of penetrating ocular wounds. In the active therapy of intraocular infections he claims that oxytetracycline does not penetrate well enough from subconjunctival depots in the low dosages that are tolerated. In order to obtain adequate vitreous levels, intravitreal injection of oxytetracycline, 250 μg./0.1 ml., is theoretically acceptable in the treatment of susceptible intraocular infection.

Lepri and Sicca[28] claim that, after local instillation of oxytetracycline in rabbits

with normal or abraded corneas, no traces of the drug could be found in the aqueous humor. Only upon the injection of 25 mg. of oxytetracycline subconjunctivally was a slight passage of the antibiotic observed, with maximum aqueous humor levels one to one and one-half hours after injection.

THE ANTIMICROBIAL ACTION OF OXYTETRACYCLINE IN VITRO

As judged by in vitro sensitivity tests, Thygeson[50] describes the antibacterial spectrum of oxytetracycline (table II).

TABLE II

The Antimicrobial Action of Oxytetracycline in Vitro

Susceptible Bacteria	
Beta hemolytic streptococci	*C. diphtheriae*
Alpha hemolytic streptococci	*K. pneumoniae*
Nonhemolytic streptococci	*H. influenzae*
Pneumococci	*H. conjunctivitidis* (Koch-Weeks bacillus)
N. gonorrhoeae	*B. anthracis*
N. meningitidis	*B. subtilis*
N. catarrhalis	*Cl. welchii*
Staphylococci	*Cl. novyi*
Moraxella lacunatus (diplobacillus of Morax-Axenfeld)	*Cl. tetani*
E. coli	*Cl. septicum*
A. aerogenes	*Cl. sporogenes*
Resistant Bacteria	
Ps. aeruginosa (some strains)	*M. tuberculosis* (some strains)
Proteus group	

The in vitro susceptibility of various species and strains of bacteria to oxytetracycline has been reported by a large group of investigators including Hobby and co-workers,[21] Sayer and co-workers,[49] Gocke and co-workers,[16] Spink,[48] Bliss et al,[9] and Bryson and Demerec.[10]

OXYTETRACYCLINE IN EXPERIMENTAL OCULAR INFECTIONS

Cannon and Leopold[11] produced experimental corneal infections with oxytetracycline susceptible strains of *Aerobacter aerogenes*, *Escherichia coli*, *Proteus vulgaris*, *Streptococcus hemolyticus*, *Staph. aureus*, and Pneumoccus type I. These lesions were treated with locally applied oxytetracycline. Oxytetracycline was successful against many varieties of organisms tested and it compared favorably with other antibiotics tested for these particular strains. The earlier therapy was instituted, the better was the result. It appears that local therapy could clear such corneal infections when instituted early. It was also apparent in these experiments that in vivo results did not always parallel in vitro sensitivity studies.

Hallett et al[17] inoculated each cornea of 7 rabbits with herpes simplex virus. One hour later treatment was started on one eye of each animal with oxytetracycline

drops, 5 mg./ml., frequently during the day and oxytetracycline ointment, 30 mg./Gm., at night. After seven days 5 of the treated eyes were definitely better than their controls; the other 2 were involved to the same extent as their controls. Six other rabbits were similarly treated with a combination of chloramphenicol and oxytetracycline. After seven days 5 eyes had the same degree of involvement as their controls and 1 was better than its control.

Geller and Thygeson[15] state that oxytetracycline drops in 2 cases of well-established herpes simplex virus infection in the rabbit appeared to modify the course of the disease. Oxytetracycline ointment used in another case produced no noticeable difference between the treated and untreated eye. Daily oral administration of 10 mg. of oxytetracycline started three days prior to or at the time of intracerebral inoculation of herpes simplex virus in mice showed no difference from the results in control mice.

Bagolini and Leonardi[4] found that oxytetracycline has no effect on the course of experimental herpes keratitis in rabbits. Herpetic material left in contact with the drug in no way reduced in virulence.

OXYTETRACYCLINE IN OCULAR INFECTIONS

Acute and Subacute Catarrhal Conjunctivitis. Thygeson[50] reported on the treatment of 73 cases of acute and subacute catarrhal conjunctivitis; 50 were treated with oxytetracycline drops and 23 with oxytetracycline ointment. The etiology was pneumococcic in 26, Koch-Weeks bacillus in 15, influenza bacillus in 11, staphylococcic in 3, and undiagnosed in 18. No resistant cases were encountered. Healing was usually complete within two to three days and always occurred within a maximum of four days. The definite reduction in the time necessary for complete cures indicates that oxytetracycline has a therapeutic effect.

Town[52] treated 48 cases of conjunctivitis due to *Staph. aureus* and/or *albus* alone or with other organisms with oxytetracycline drops every two hours. Some of these cases had associated blepharitis and/or keratitis. Infection cleared in 24 to 48 hours, although a few lasted one to four weeks. A few recurred when treatment was stopped but cleared on further treatment. The symptoms of burning and itching stopped almost immediately. Seven additional cases of pneumococcic conjunctivitis cleared in two to four days; recurred but cleared after ten more days of treatment. Two streptococcic cases cleared in three days, 6 Koch-Weeks cases cleared in one to three days, and 6 Morax-Axenfeld infections were relieved of symptoms in two to four days. One combined staphylococcus and streptococcus case was resistant.

Douvas et al[13] listed 33 cases of bacterial conjunctivitis (mostly hemolytic *Staph. aureus*, a few alpha hemolytic streptococci, and *Diplococcus pneumoniae*) treated with oxytetracycline drops, 5 mg./ml. every two hours and 0.1 per cent ointment at bedtime or ointment alone four times daily. Thirty cases were greatly improved or clinically cured after 24 to 48 hours, 2 more, on ointment alone, needed three days, and one very severe case needed five days.

Bhaduri and Agarwalla[5] treated 52 cases of acute catarrhal conjunctivitis (no cultures were made) with a single daily application of oxytetracycline drops and ointment. After four applications 18 cases were cured; after 7 to 10 applications 32 more were cured; and the last 2 cases did not respond but were ameliorated.

Bartolome[6] states that in all forms of acute conjunctivitis treated with oxytetracycline the results were surprisingly good.

Chronic Catarrhal Conjunctivitis. Thygeson[50] treated 43 cases of chronic catarrhal conjunctivitis with oxytetracycline solution or ointment. He found coliform rods in 9 cases, *Proteus ammoniae* in 2, diplobacilli in 3, *Neisseria catarrhalis* in 2, and undetermined in 27. The treatment was effective in the coliform, diplobacillary, catarrhalis, and 7 of the undetermined (3 of these relapsed). He concludes that oxytetracycline is only as good as other antibiotics or sulfacetimide for chronic conjunctivitis. Bartolome,[6] too, states that treatment with oxytetracycline is rather disappointing in chronic conditions.

Bhaduri and Agarwalla[8] list 36 cases of chronic catarrhal conjunctivitis, including a few cases of angular conjunctivitis, which were treated by a once daily application of oxytetracycline drops and ointment. Complete cures were obtained in an average of about three days, although 7 cases required one week.

Ophthalmia Neonatorum. O'Brien[36] defined ophthalmia neonatorum as a definite purulent conjunctivitis in newborn infants. Female infants were used as controls, the lids being wiped gently with small dry sterile squares of white lint immediately after birth. In males the lids were similarly cleansed and 2 drops of oxytetracycline solution, 5 mg./ml., or about 30 mg. of oxytetracycline ointment, 1 mg./100 Gm. were instilled in each conjunctival sac. Of 254 drop-treated cases 2.9 per cent developed ophthalmia as against 4 per cent of 264 controls. Of 270 ointment treated cases 4.5 per cent developed ophthalmia as against 7 per cent of 259 controls. The difference between the treated and untreated cases is believed to be insignificant in both groups.

Wolman and Holzel[64] treated 12 newborn babies suffering from purulent conjunctivitis due to coagulase-positive *Staph. aureus* (7 of the 12 being resistant to penicillin) with oxytetracycline drops, 5 mg./ml. The drops were instilled in each eye, 1 drop every minute for five minutes, followed by 1 drop every two minutes for 10 minutes, the whole procedure being repeated three times daily. Six out of 7 cases classified as mild, 3 classified as moderate, and 2 severe cases improved within 48 hours.

Thygeson[50] instilled oxytetracycline ointment four times daily in 6 cases of ophthalmia neonatorum, 1 due to inclusion blenorrhea and 5 to staphylococci. All cases cleared in 48 hours.

Follicular Conjunctivitis. Both Thygeson[50] and Douvas et al[13] treated 2 cases each of Beal's conjunctivitis with oxytetracycline to no avail even up to 8 days of therapy.

Thygeson[50] treated 1 case of inclusion conjunctivitis with oxytetracycline ointment six times daily for one week. A rapid response was obtained and inclusions were not demonstrable after the second day of treatment. He also found oxytetracycline ineffectual in 4 cases of chronic folicular conjunctivitis of unknown etiology and 8 cases of folliculosis in children. Town[52] lists 6 cases of follicular conjunctivitis, in which no bacteria were isolated, that cleared in two days on oxytetracycline treatment.

Trachoma. Mitsui et al[31–33] treated about 700 cases of trachoma with oxytetracy-

cline. An ointment appeared more effective than a solution; systemic administration is inadequate because a high local concentration of the antibiotic is required. In acute trachoma clinical cure results in two to three weeks, but to prevent relapse, treatment should be continued for another two weeks. Chronic trachoma takes at least one month (in some cases two months or more) of treatment to eradicate the causative agent. In the late stage of trachoma, it is advisable to have a second course of treatment five or six months after beginning the first course.

Agarwal and Gupta[1] treated 50 trachomatous patients in the infiltrative or follicular stage who showed inclusion bodies with oxytetracycline drops 2.5 mg./ml. three times daily and 1 per cent ointment at bedtime daily for six weeks and one capsule every six hours for one week. Subjective improvement started within 24 hours and secondary infection cleared within 48 hours in all cases. In 6 cases the pannus retrogressed in about two weeks and the inclusion bodies disappeared from the conjunctival scrapings at the end of three weeks. In 6 more cases the pannus retrogressed in four weeks and the inclusion bodies disappeared at the end of six weeks. The cure rate was 24 per cent.

Naccache[31] treated 36 cases of trachoma for three months with 0.5 per cent oxytetracycline ointment. Six cases of trachoma I and 7 cases of early trachoma II were cured. Of 15 cases of late trachoma II, 2 were greatly improved. Eight cases of trachoma III were moderately improved.

Thygeson[50] treated 11 cases of trachoma in various stages with oxytetracycline ointment four to six times daily for three to eight weeks. There was dramatic improvement in all with apparent healing in 9 cases. Lepri[26] claims that 7 cases of trachoma treated with oxytetracycline responded fairly favorably although inferiorly to chlortetracycline.* Lepri and Von Berger[27] in 18 cases of acute trachoma treated one eye with oxytetracycline and the other with chloramphenicol; oxytetracycline was very effective but not much more so than chloramphenicol. Town[52] treated 1 case of trachoma with oxytetracycline, producing subjective improvement in three days and clinical improvement by eight days. Siniscal[43] states that local or systemic oxytetracycline is very effective in clearing the common secondary infections concurrent with trachoma but fails to clear the early pannus, to relieve turgescence of the retrotarsal folds, to resolve granules, or to decrease lacrimation and itching. Kamel[22] claims oxytetracycline is effective in the treatment of trachoma. Nquyen[35] feels that oxytetracycline is not a specific drug for trachoma, although it has a remarkable action on the secondary infections complicating the disease.

Chronic Membranous Conjunctivitis. Both Thygeson[50] and Winter and Michler[53] report 1 case each of chronic membranous conjunctivitis. Thygeson treated his case with ointment and systemic oxytetracycline for two weeks without benefit. The other case yielded a heavy growth of type VII pneumococcus and coagulase-negative *Staph. albus*. Bacterial cultures became negative after two days of penicillin, but the membranes persisted. Local and systemic oxytetracycline was then given for 16 days with some diminution in the rapidity of the growth of the membrane.

* The trade name of Lederle Laboratories Div., American Cyanamid Co., for chlortetracycline is Aureomycin.

Lacrimal Sac Affections. Thygeson[60] treated 3 beta hemolytic streptococcal and 1 *Staph. aureus* acute dacryocystitis cases with full therapeutic doses of oxytetracycline systemically. There was a rapid subsidence of inflammation but surgical relief of stenosis was later required. In 7 cases of adult chronic dacryocystitis with lacrimal obstruction plus *D. pneumoniae* in 6 and *Hemophilus influenzae* in 1, oxytetracycline produced some decrease in secretion but no permanent benefit. In 9 cases of congenital dacryostenosis and dacryocystitis in newborns, 6 presenting *D. pneumoniae* and 3 *H. influenzae*, oxytetracycline ointment four times daily produced no permanent effect.

Bartolome[8] successfully treated 7 cases of dacryocystitis with oxytetracycline within seven days but 5 of these became reinfected after approximately three months Town[62] found that oxytetracycline cleared 3 cases of chronic dacryocystitis (1 being congenital) in one week withour recurrences.

Blepharoconjunctivitis. In 2 cases of blepharitis due to *Staph. aureus* resistant to sulfacetimide and penicillin, Ainslie[2] obtained immediate improvement with 0.1 per cent oxytetracycline ointment. Town[62] states that 1 case of severe blepharitis associated with severe seborrhea responded much better to oxytetracycline than to anything previously used.

Thygeson[60] treated 120 cases of blepharoconjunctivitis with oxytetracycline and found that only the diplobacillary cases respond completely; the staphylococcal and seborrheic cases respond only partially. In staphylococcal blepharitis the presence

TABLE III

Topical Administration of Oxytetracycline Ointment and Aqueous Solution in Blepharoconjunctivitis

No. Cases	Etiology	Healed	Improved	Unimproved	Remarks
47	Staphylococcic:				
	with meibomitis, 26;	2	18	6	Frequent relapses
	without meibomitis, 21	8	12	1	Occasional relapses
31	Seborrheic	0	19	12	Definitely inferior to ammoniated mercury-salicylic acid ointment
18	Mixed staphylococcic and seborrheic: with meibomitis, 10;	0	6	4	Marked tendency to relapse
	without meibomitis, 8	2	6		
5	Diplobacillary	5			No relapses
2	Mixed staphylococcic and diplobacillary	2			One relapse
19	Undetermined	2	10	7	Occasional relapses

of meibomianitis seems to lower the percentage of clinical and bacteriologic cures. Seborrheic blepharitis is a stubborn therapeutic problem, easy to improve but very difficult to cure. Table III breaks down his results.

Hordeolum. Bartoleme[6] claims that in recurrent styes oxytetracycline prevents recurrences, but it has no effect on the acute stage. Thygeson[50] treated 19 cases of internal and external hordeolum topically with oxytetracycline. This produced no effect on the course of the disease but the common secondary involvement of other glands did not occur. Town[52] treated 8 cases of infected chalazia with oxytetracycline; 3 early ones cleared spontaneously in 3 to 5 days, the others had to be excised.

Impetigo. Town[52] cured in 3 days 1 staphylococcal conjunctivitis associated with impetigo by oxytetracycline drops and 250 mg. orally every six hours. Thygeson's[50] 3 cases of impetigo involving the face and eyelids responded dramatically and completely to oxytetracycline.

Infectious Eczematoid Dermatitis of the Lids. Three cases of this condition, due to *Staph. aureus*, responded in Thygeson's[50] experience promptly and completely to oxytetracycline ointment.

Allergic Conjunctivitis. Bhaduri and Agarwalla[8] treated 6 cases of phlyctenular conjunctivitis once daily with oxytetracycline drops and ointment and obtained relief of symptoms in two days and disappearance of signs in two more days. Thygeson[50] in 6 cases of phlyctenular keratoconjunctivitis without secondary infection obtained no effect from oxytetracycline drops, but in 2 secondarily infected treatment with drops and ointment produced a good response within 48 hours. Thygeson also found that 7 cases of vernal catarrh were not ameliorated by oxytetracycline; 4 other cases with secondary infection, however, did benefit but were not arrested. He also found that 5 cases of hay fever conjunctivitis were not affected by oxytetracycline.

Ocular Pemphigus and Erythema Multiforme. Thygeson[50] freed a case of ocular pemphigus from secondary pneumococcic and staphylococcal infection by oxytetracycline ointment with considerable relief but no improvement in the underlying cicatrizing disease. Thygeson[50] also mentions 3 cases of conjunctival cicatrization due to previous membranous conjunctivitis in erythema multiforme. All 3 cases were heavily infected with *Staph. aureus* and all improved upon treatment with oxytetracycline solution.

Keratitis. Bhaduri and Agarwalla[8] list 7 cases of keratitis, 4 of superficial keratitis, and 3 of phlyctenular keratitis, which they treated with oxytetracycline ointment four times daily. The 4 cases of superficial keratitis were cured in six days and 2 of the phlyctenular cases in four days. The last case did not respond. Town[52] mentions 1 case of filamentary keratitis that cleared in two days from local and oral oxytetracycline.

Marginal Corneal Ulcers. Town[52] treated 15 cases of superficial punctate keratitis and marginal corneal ulcers with oxytetracycline. Four were promptly relieved but 3 recurred as soon as the treatment was stopped. In 7 cases there was no response. One case associated with an allergy cleared in one month. Douvas et al[13] reported that 3 patients with marginal corneal ulcer (hemolytic *Staph. aureus* cultured in 2) had no corneal staining in two to four days after oxytetracycline treatment was started. In Thygeson's[50] series of marginal corneal ulcers 6 staphylococcal and 1 diplobacillary cases were aided; 4 staphylococcal, 3 seborrheic, and 3 endogenous cases were not helped.

Central Corneal Ulcers. Bhaduri and Agarwalla[8] treated 14 cases of corneal ulcer

with oxytetracycline ointment 4 times daily. Most cases cleared in 10 days. Post-variolar and post-traumatic ulcers responded well. Bartolome[6] obtained excellent results in simple corneal ulcers following conjunctivitis and in hypopyon ulcers. Town[52] treated 2 cases of *Bacillus proteus* corneal ulcers without any appreciable effect from oxytetracycline. Douvas et al[13] treated 4 cases of fingernail abrasions of the cornea prophylactically with oxytetracycline without complications. Thygeson[50] treated 34 cases after corneal foreign body removal prophylactically with oxytetracycline ointment without complication. He also obtained prompt healing of 3 cases of central pneumococcic ulcers with local treatment in 2 cases and local plus systemic oxytetracycline in the third case.

Keratoconjunctivitis Sicca. Town[52] kept one case of keratoconjunctivitis sicca with positive *Staph. aureus* culture symptom free for one month on oxytetracycline, but afterward the drug was of no avail. Thygeson[50] treated 6 cases with oxytetracycline drops 6 times daily without improvement, although 2 cases with secondary staphylococcal infection were greatly improved.

Rosacea Keratoconjunctivitis. Thygeson[50] reports 3 cases with mild epithelial keratitis and positive *Staph. aureus* cultures, which improved on oxytetracycline drops without complete relief. Two other cases with recurrent marginal ulcers secondary to staphylococcal blepharoconjunctivitis were treated with oxytetracycline drops and ointment resulting in control of the disease.

Viral Infections. 1. Herpes Simplex. Douvas et al[13] treated 3 cases of dendritic keratitis ineffectively with oxytetracycline. Town[52] cleared 1 case of dendritic ulcer in two days, but another severe case failed to respond to oxytetracycline. Thygeson[50] treated 11 cases of dendritic keratitis with oxytetracycline drops hourly and ointment at night; 2 healed in four days, but 9 needed iodine cauterization. He also treated 2 cases of acute herpetic keratoconjunctivitis unsuccessfully with oxytetracycline. Sorsby[46] claims that oxytetracycline did not improve dendritic ulcer or disciform keratitis. Bartolome[6] also reported unsuccessful therapy with oxytetracycline in 2 cases of dendritic keratitis.

2. Herpes Zoster Ophthalmicus. Town[52] claims that a case of keratitis in herpes zoster obtained immediate relief with oxytetracycline. Thygeson[50] treated 3 cases with systemic and topical oxytetracycline and concluded that he prevented the secondary infection of the skin vesicles but produced no clear-cut effect on the corneal disease. Bartolome[6] obtained variable results in the treatment of herpes zoster with oxytetracycline. Herrell et al[19] found no demonstrable effect in one case of herpes zoster.

3. Epidemic Keratoconjunctivitis. Thygeson[50] found no effect from treatment with oxytetracycline in 5 cases of epidemic keratoconjunctivitis. Sorsby et al,[47] however, claim that that disease responds well to oxytetracycline. Lepri[26] states that oxytetracycline has no effect in epidemic keratoconjunctivitis except perhaps to shorten the course of the disease slightly.

4. Superficial Punctate Keratitis. Thygeson[50] reported 3 cases of superficial punctate keratitis without secondary infection that obtained no relief of signs or symptoms after oxytetracycline drops hourly for one week. Lepri[26] claims 1 case was quickly and favorably influenced by oxytetracycline.

5. Molluscum Contagiosum Conjunctivitis. Thygeson[50] also treated 1 case of this disease with oxytetracycline without effect.

6. Newcastle Virus Conjunctivitis. Thygeson[50] also treated 1 case of this disease with oxytetracycline, again without effect.

7. Parinaud's Conjunctivitis. Town[52] lists 2 cases of Parinaud's conjunctivitis of virus etiology that he treated with oxytetracycline. One was cured in 2 weeks, the other failed to respond.

Uveitis. Bhaduri and Agarwalla[5] treated 5 cases of iritis with atropine and oxytetracycline drops and obtained cures in five days. Thygeson[50] gave oral oxytetracycline in full therapeutic dosage in 8 cases of chronic granulomatous uveitis and in 2 cases of uveitis and hypopyon. No significant results were obtained in the granulomatous cases, and, although improvement occurred during treatment in the 2 nongranulomatous cases, the change was insufficient for definite conclusions.

Episcleritis. Bhaduri and Agarwalla[5] found no effect after 10 days of treatment with oxytetracycline in 2 cases of episcleritis. Douvas et al[13] treated 1 case with oxytetracycline and obtained a clinical cure in two days.

Traumatic and Surgical Infections. Douvas et al[12] ordered 0.1 per cent oxytetracycline ointment four times daily for three days preoperatively in 110 patients. Positive cultures for ophthalmic pathogens (hemolytic *Staph. aureus*, alpha hemolytic streptococcic, and *D. pneumoniae*) were found in 37 instances. Second cultures made after three days of treatment yielded no pathogens and no cases of postoperative infection occurred in the entire group. Town[52] reported 1 case in which a preoperative streptococcic culture was found; treatment with oxytetracycline produced a negative culture one week later. Town also lists 5 ocular infections following trauma which cleared in three days without complication upon treatment with oxytetracycline.

Thygeson[50] records 2 cases of severe fulminating infection following cataract extractions. The offending organisms were not found but treatment with penicillin and oral oxytetracycline produced a good response and useful vision was recorded. In cases of this sort reference may also be made to Leopold's[28] advice as already discussed under intraocular penetration of oxytetracycline. Thygeson[50] also lists 2 cases of acute glaucoma with associated staphylococcal blepharitis treated prophylactically with oxytetracycline before required intraocular surgery and resultant uncomplicated convalescence. One case of atopic dermatitis and keratitis with coagulase-positive staphylococci in the conjunctiva and lid margins was treated prophylactically with oxytetracycline before keratoplasty with uneventful postoperative recovery.

Locatcher-Khorazo[29] with a view to selecting a suitable preoperative sterilizing agent compared 1 per cent chloramphenicol, 0.5 per cent oxytetracycline, and an ointment containing 1000 units penicillin G potassium and 20 mg. streptomycin per Gm. She found that the penicillin-streptomycin ointment sterilized the conjunctiva in 24 to 72 hours in 157 patients. The other two antibiotics were far less effective even over longer periods of time. She also claims that the penicillin-streptomycin ointment clears up chronic eye infections much more rapidly than chloramphenicol or oxytetracycline.

Toxoplasmosis. Eyles and Coleman[14] found that oxytetracycline shows slight but statistically significant chemoprophylactic activity in mice infected with a strain of toxoplasma isolated from rats. Chlortetracycline appears more active, but even here doses higher than are attainable in man had to be used prophylactically. Strains of toxoplasma differ in their response to various drugs.

Venereal Diseases. Schoch and Alexander[41] claim that oxytetracycline is very effective in gonorrhea, definitely in primary syphilis, and only partially effective for granuloma inguinale. Thygeson[51] points out that oxytetracycline is active against the virus of lymphogranuloma venereum.

Brucellosis. Knight[24] states that oxytetracycline is useful in alleviating the symptoms of acute brucellosis but fails to free the host entirely of the causative bacillus. It is bacteriostatic rather than bactericidal. Oxytetracycline treatment is useful in assisting the patient's defense mechanism to combat the infection in conjunction with other treatment.

Tuberculosis. Hobby et al[20,21] found that *Mycobacterium tuberculosis* is susceptible to the action of oxytetracycline in vitro. Steenken and Wolinsky[49] showed that oxytetracycline has definite antituberculous activity in guinea pigs and mice infected with streptomycin-resistant human tubercle bacilli.

Reiter's Disease. Keefer[22] lists Reiter's disease among those conditions in which oxytetracycline has a partial effect.

Tularemia. Keefer[22] also lists tularemia among the diseases in which oxytetracycline has a partial effect. Bauer et al[7] state that the protective index in mice infected with *Bacillus tularensis* and treated with oxytetracycline is high.

Bacillus proteus *and* Pseudomonas aeruginosa *Infections.* Keefer[22] lists these infections among those in which oxytetracycline is ineffective. Baker and Pulaski[5] showed that *B. proteus* in heavy growth dominates the fecal flora as other organisms disappear after ingestion of oxytetracycline. Hammond and Miller[18] found that in irradiated mice oxytetracycline affords a good deal of protection from septicemia due to intestinal bacteria, except *Pseudomonas.* Schoenbach et al[42] were unable to control with oxytetracycline urinary tract infections due to *B. proteus* or *Bacillus pyocyaneus.*

Rickettsial Infections. Snyder et al,[45] Smadel et al,[44] and Rose [39] have shown that oxytetracycline has a positive effect in experimental and clinical rickettsial infections.

SUMMARY

It is apparent from experimental and clinical studies that oxytetracycline can be used successfully in the therapy of external ocular infections caused by susceptible strains of organisms. These include many species of bacteria, viruses, and rickettsiae. Because of its low intraocular penetration this agent has not been recommended or tried experimentally on a large scale for intraocular infections.

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GENERAL PRACTICE CLINICS

This monthly section of General Practice Clinics features reports of papers delivered at current medical meetings in the United States and abroad.

Nasal Hydrocortisone in Allergic Rhinitis: A Controlled Study

Presented by HENRY D. OGDEN, M.D., HULDAH BANCROFT, M.D., JACK BULL, M.D., WILLIAM STEVENS, M.D., CECIL BRANSON, M.D., AND C. A. BODET, JR. (New Orleans, La.) before the American Academy of Allergy, 11th Annual Meeting, New York City, Feb. 7, 1955.

The effect of nasal hydrocortisone in allergic rhinitis was studied using the inactive diluent as a blind control placebo. The solution was 15 mg./cc. of hydrocortisone acetate. No vasoconstrictors, antihistamines or antibiotics were added. Initially, dosage was one instillation from a plastic spray bottle into each nostril, four times daily (approximately 12 mg. hydrocortisone per day). Later dosage was 2 instillations in each nostril five times daily (30 mg. hydrocortisone). Patients were given (1) hydrocortisone only, (2) placebo only or (3) alternate hydrocortisone and placebo. They were evaluated according to subjective symptoms (sneezing, phlegm in throat, nasal discharge, blockage and itching) and objective symptoms (color of mucosa, size of turbinates, degree of bogginess, nasal polyps, postnasal drip) expressed by a weighted score.

With the smaller dose, from the objective standpoint, 16 patients observed during nine weeks showed a score of 0.74 before treatment, a weekly score of 0.62 during treatment. Placebo controls (10 patients, 10.7 weeks) showed a pretreatment score of 0.84, weekly score during treatment of 0.67. Over-all score for all subjective symptoms was 0.63 in the hydrocortisone patients, 0.90 in controls. Differences were not regarded as statistically significant but there were lesser symptoms in hydrocortisone group in all categories. With the larger dose (28 hydrocortisone treated 4.4 weeks; 27 controls, 4.8 weeks), over-all subjective scores were 0.72 for hydrocortisone, 0.76 for controls. Investigators felt that benefits in all cases were due entirely to local action. There were no systemic effects or untoward reactions in any patient.

The authors feel that the time of contact of hydrocortisone might have been too short. They suggest application in water-soluble jellies or impregnated packs. In a preliminary study with cotton packs impregnated with 1.5 per cent hydrocortisone, 40 patients were treated by placing packs in the middle meatus for 30 minute periods, sometimes for 3 consecutive days. There were no controls. There was indication of improvement in a number of these patients. In one patient treated

with hydrocortisone pack in 1 nostril, saline pack in the other, there was slight decrease in size of the nasal turbinates in the hydrocortisone treated side. In a small group of patients, good results seemed to be obtained when the spray was used more frequently during the first 48 hours.

Cortisone or Hydrocortisone in the Treatment of Severe Intractable Bronchial Asthma

Presented by WALTER S. BURRAGE, DAVID M. K. WANG, JOHN W. IRWIN, AND SAUL ARONOW (Medical Service of the Massachusetts General Hospital and the Department of Medicine, Harvard University), before the American Academy of Allergy, 11th Annual Meeting, New York City, February 7, 1955.

A study was made of the dosage of cortisone and hydrocortisone required for complete suppression of subjective symptoms of bronchial asthma and for maintenance of patients after such suppression. Beginning with 6 patients, a final group of 18 were given cortisone for suppression of symptoms. Eight of these were transferred to hydrocortisone and 6 new patients were given hydrocortisone only. All patients were complete invalids. The total initial oral dose of cortisone required to aid the patient (initial clearing dose) was 1,127 mg. (plus or minus 137 mg.); that of hydrocortisone was 1,231 mg. (plus or minus 181 mg.). The difference was not statistically significant. The compounds were equally effective in rendering the patient free of symptoms initially. The daily maintenance dose of cortisone was about 73 mg.; that of hydrocortisone about 51.6 mg., figures that did prove statistically different. Some patients were treated for more than 4 years with little change in the maintenance dose, except during periods of stress or respiratory tract infection.

Gonorrhea in the Female

Presented by GEORGE W. MITCHELL, M.D. (Tufts Medical College), before the Massachusetts Department of Public Health, New England Center Hospital, Boston, Mass., February 15, 1955.

When the gonococcus enters the female genitourinary tract, Bartholin's and Skene's glands at the entrance of the vagina are often first infected. The vaginal mucosa is resistant to gonorrheal infection except in children and postmenopausal women. The glands of the cervix are next invaded, causing an acute cervicitis. Some students of the disease believe that the gonococcus can remain dormant for a long time in the glands of the cervix and vagina acting as foci for reinfection. The endometrium is resistant to the disease. There is a transient, acute endometritis as a result of retrograde spread of the infection, but it is difficult to culture gonococci from the endometrium. The infection then spreads along the tubes.

If the tubes remain patent, pus formed by the infection can drain into the pelvic peritoneum, causing a localized peritonitis which may later become generalized. When the tubes are blocked, pyosalpinges develop. Usually both sides are involved. As the acute infection subsides, the pyosalpinges may become hydrosalpinges. The ovarian parenchyma is rarely infected, but peri-ovarian abscesses are common. Occasionally at the time of ovulation, bacteria directly invade the ovaries. Large tubo-ovarian abscesses or separate pelvic abscesses in the rectovaginal space are later manifestations of the disease.

The diagnosis is made on the basis of a history of gonorrheal contact, plus either smears or cultures positive for Neisseria gonorrheae. The early symptoms are purulent vaginal discharge, pain due to abscesses of Skene's or Bartholin's glands, or pelvic pain as a result of inflammation of the tubes or peritonitis. The late symptoms include aberrations in the menstrual cycle, usually in the form of excessive bleeding, pain due to the sequelae of peritonitis and pelvic abscesses, and sterility. The early clinical signs are the finding of tender, swollen vulvovaginal glands and a red, edematous cervix exuding a thick yellow discharge. However, there is nothing distinctive about gonorrheal cervicitis to differentiate it from cervicitis of other etiology. Later clinical signs may include fever, rapid pulse, exquisitely tender abdomen with involuntary muscle spasm, pain on motion of the cervix, or tender, thickened adnexa. A large pelvic abscess is usually palpated best per rectum. If untreated in the early stages, the pelvic infection may subside spontaneously or progress to produce the late changes previously described. Laboratory methods of diagnosis are still somewhat unsatisfactory; and for the greatest possible accuracy, smears and cultures must be obtained early in the course of the disease, since the organism is a frail one and usually does not persist in the genital tract longer than a week or ten days. It is probable that secondary pyogenic invaders cause most of the serious damage.

Penicillin has proved highly effective in the treatment of gonorrhea; and if given early assures complete cure in 95 per cent of the cases. Because of this, the number of cases of sterility due to gonorrhea has greatly decreased in recent years. When walled-off abscesses have developed in the tubes or in the pelvis, penicillin and other antibiotics are chiefly effective in preventing further spread of the disease. In such cases, surgical intervention may be indicated to promote adequate drainage or to remove the affected parts.

Current Status of Rauwolfia Preparations

Presented by GEORGE A. HELLMUTH, M.D. (Milwaukee County General Hospital) before the Chicago Medical Society, Nov. 12, 1954.

The principal advantage of Rauwolfia serpentina over other hypotensive drugs is its relative lack of toxicity. Rauwolfia can be combined effectively with the more potent antihypertensive drugs and in such combination the latter drugs produce fewer untoward side effects. Rauwolfia is most useful in the treatment of patients with mild, labile, and neurogenic types of high blood pressure. In com-

bination with other hypotensive drugs, its action allows a more effective therapeutic approach to the more severe forms of hypertension.

The principal effect is a central vasodepression action. In addition, adrenergic blockage, sedative action and the ability to slow the pulse rate without postural hypotension or disturbing renal effects, are distinct advantages in the use of this drug. Mild reactions to Rauwolfia such as stuffiness of the nose, drowsiness, and laxative effect are common; nausea and vomiting occur occasionally; nightmares are infrequent. An increased appetite with a gain in body weight and a sense of well-being are common occurrences. The hypotensive state appears slowly, usually within three to seven days but occasionally it may be as late as three or four weeks. After withdrawal, the action of the drug may last several weeks.

Simple uncomplicated labile hypertension with a diastolic level of 100 to 120 mm. Hg., especially if associated in a young individual with anxiety and increased pulse rate, responds best to Rauwolfia. About 40 to 50 per cent of these cases, after three to four weeks therapy, show significant lowering of the blood pressure. Significant lowering of the blood pressure occurs when the average mean blood pressure is reduced by 20 mm. Hg. Mean blood pressure is calculated by adding one third of the pulse pressure to the diastolic level.

A persistent and stable hypertension at the above diastolic level may require four to five weeks of continuous drug therapy before adequate reduction occurs. Fixed hypertension with a diastolic pressure between 120 and 140 mm. Hg., without evidence of renal involvement, should receive hydralazine (Apresoline) if the blood pressure fails to respond after one month of Rauwolfia therapy. A significant number of failures with the use of Rauwolfia alone will respond adequately to combined therapy. The combined use ameliorates such side effects of hydralazine as tachycardia and headache. Smaller dosages of hydralazine frequently become effective with this method of treatment.

If the mean blood pressure fails to be reduced and appears to be progressive, or the diastolic blood pressure is higher than 140 mm. Hg., one may consider the combined use of a methonium preparation with or without hydralazine. The use of Rauwolfia alone in severe hypertension is ineffective in more than 80 per cent of the cases. The author warns that considerable caution should be exercised when hexamethonium is given. The problem of drug tolerance, postural hypotension, constipation, urinary bladder retention and impaired eye accommodation, although lessened, still present serious difficulties. Pentalinium is a new and more effective methonium hypotensive agent. It can be readily used by mouth. It is most effective in combination with Rauwolfia and hydralazine. Pentalinium is a powerful antihypertensive drug and is especially valuable in the treatment of malignant and severe forms of hypertension.

Veratrum (Veriloid) presents serious toxic problems because of its narrow margin of therapeutic safety. Its use should be reserved for severe forms of elevated blood pressure including hypertensive encephalopathy and cases associated with renal impairment. The combined uses of Rauwolfia, hydralazine and veratrum may be well tolerated.

The Enlarged Spleen

Presented by PROF. MILNES WALKER (Bristol University, England), before the College of Physicians and Surgeons of Saskatchewan, Canada, October 5, 1954.

The author pointed out that portal hypertension is the second most common cause of hematemesis (10 per cent) the first being peptic ulcer (90 per cent). Mortality from hematemesis associated with portal hypertension is high because the bleeding points in the esophageal varices are not accessible, and are under a high head of pressure.

Portal hypertension is generally the result of obstruction to portal flow either in the intra- or extra-hepatic regions. In the extrahepatic region, tumor metastases, lymph nodes, congenital abnormalities and thrombosis of the portal vein may be the cause. Cirrhosis of the liver is the most common intrahepatic cause. With obstruction to portal flow there is a three to four times increase in portal venous pressure, and the development of an extensive venous collateral circulation to bypass the obstructed area. It is the rupture of the dilated venous collaterals in the lower end of the esophagus which is responsible for the fatal and alarming hemorrhage in portal hypertension.

The author has used portal venography to study the nature of the obstruction in portal hypertension and to gain information concerning the state of the veins which is important in planning surgical treatment. Contrast medium is injected into the spleen and fills the portal bed. It demonstrates whether the obstruction is intra- or extra-hepatic and also affords important information about the patency of the portal vein. The author employs a wide anastomosis between the portal vein and the inferior vena cava (end to side). He has found this superior to the splenic vein-renal vein shunt, and regards it as the operation of choice. He actually constructs a very good sized Eck's fistula. Following this pressure in the portal system falls dramatically, the collaterals and esophageal varices collapse and there is an immediate decrease in the size of the spleen. Full regression of the spleen takes many months, as the effects of chronic hyperemia in the spleen are slow to disappear. In addition, the author has noted disappearance of the hematologic disorder of "hypersplenism" in some patients treated in this way. Contrary to the results with animal work, no metabolic disorders of any note have followed on the construction of this bypass around the liver.

Gonorrhea in the Male

Presented by B. G. CLARK, M.D. (Tufts Medical School) before the New England Center Hospital, Boston, February 15, 1955.

In the male, the primary gonococcal infection is an acute urethritis. Gonorrhea, per se, is a self-limited disease even without treatment. The patient's immunogenic

response is indicated by the development of positive complement fixation reactions. In untreated cases, after some weeks or months, mixed and nonspecific infections of the urethral and prostatic glands displace and supplant the gonococcal infection. The proximity of the urethral glands to the sinusoids of the corpus spongiosum facilitates hematogenous distribution of gonococci. Gonococcal endocarditis and arthritis, though uncommon, must be considered in the differential diagnosis of endocardial or joint infections.

The treatment of choice for acute gonococcal urethritis in the male is intramuscular injection of 600,000 units of a repository preparation of penicillin. Cure rates of 95 to 98 per cent may be expected.

The Tongue in Health and Disease

Presented by LEO STERN, D.D.S. (Department of Dental and Oral Surgery. The Mount Sinai Hospital), before the Symposium on The Tongue in Health and Disease, New York, January 26, 1955.

In the clinical examination of the tongue, feel as well as sight must be employed to detect variations in size, color, texture as well as masses and superficial lesions. A routine systematic examination would include (1) Elevate tongue with the tip to the palate and examine the ventral surface; (2) Protrude the tongue to examine dorsum; (3) Grasp the tongue and rotate to examine the lateral margins; (4) Palpate with a "rolling squeezing motion" to determine consistency and masses. A papilloma should be palpated to determine consistency of surface, edges and base.

The normal tongue ventral surface is covered with a thin epithelial coating through which are seen veins and muscle striations. It is always moist even in the dehydrated patient. Because of its protected position, it escapes major trauma, and lesions are rarely seen here. The dorsum is exposed to trauma and many of the tongue lesions are found here. Normally, the papillae are evenly distributed and tend to disappear at the lateral edges. Symmetrical fissures appearing as smooth coated depressions occur normally. Unsymmetrical, more wrinkled depressions are more likely to be scars.

Furring of the tongue represents oral debris caught between papillae and occurs in both health and disease. Furring is also seen in the early stages of vitamin deficiency. Hypertrophy of papillae is produced by irritants such as antibiotics which can produce elongated and discolored filiform papillae. Total depapillation, or smooth tongue, is found in anemias, luetic glossitis, and nutritional deficiencies.

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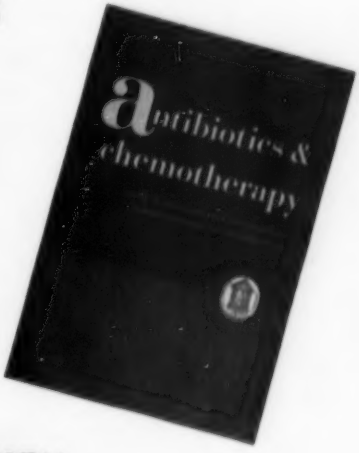

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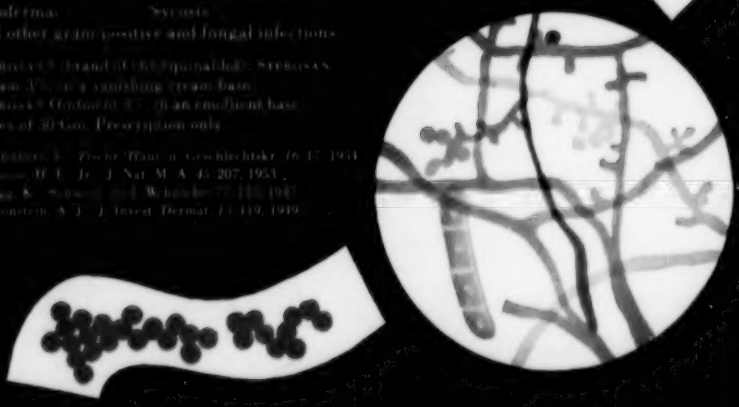

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